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N-(Phosphonacetyl)-L-aspartate (PALA) in Advanced Soft Tissue Sarcoma: a Phase II Trial of the EORTC Soft Tissue Sarcoma Group*

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Abstract—*Thirty-six patients with measurable or evaluable advanced soft tissue sarcoma were entered in a phase II trial with PALA. Among the 27 evaluable patients, 15 were men, the median age was 55 yr (16–69) and the median performance status (Karnofsky) was 80 (50–100). Most patients had leiomyosarcoma (8), liposarcoma (3), neurofibrosarcoma (3), synovial cell sarcoma (3), or undifferentiated sarcoma (3). Indicator lesions consisted essentially of lung metastases (21) and/or soft tissue lesions (14). All patients had received prior chemotherapy with 1–5 regimens and 6 had achieved objective response with these previous treatments. PALA was given as a 60-min i.v. infusion at a daily dose of 2.5g/m² for two consecutive days. Courses were repeated every two weeks. A median number of 3 courses (2–17) were administered. Partial remission (>50%) was obtained in one patient with a liposarcoma who had also responded to prior combination chemotherapy. This single response to PALA lasted 6 weeks from initiation of therapy. Four patients had unchanged disease after 6+ courses of PALA and 22 had progressive disease. Toxic effects were generally mild to moderate and included cutaneous toxicity (17), diarrhea (14), stomatitis (13), ocular manifestations, consisting of conjunctivitis, corneal ulceration and/or photophobia (11), nausea and vomiting (6) and, possibly, seizures (2). There was no evidence of drug-related myelosuppression. It is concluded that PALA given at the dose schedule selected for this trial has no significant antitumor activity in advanced soft tissue sarcoma previously treated with chemotherapy.*

INTRODUCTION

N-(PHOSPHONACETYL)-L-ASPARTATE (PALA) is a potent inhibitor of aspartate transcarbamylase, a key enzyme in the *de novo* biosynthesis of pyrimidine nucleotides [1]. This inhibition results in cytotoxic effects which may be reversed *in vivo* by uridine and carbamyl-DL-aspartate [2]. In mice, PALA is active against a variety of solid tumors [3, 4], particularly the Lewis lung carcinoma [5], whereas L1210 and P388 leukemias are relatively or completely resistant to the drug. This unusual spectrum of antitumor activity has been related to a direct relationship between drug resistance, cellular levels of aspartate transcarbamylase and cell proliferation rate [3, 6]. Cellular uptake mechanisms and pyrimidine salvage pathways might also interfere with the cytotoxic properties of the drug [7].

In humans, pharmacokinetic studies revealed a biexponential plasma disappearance curve and a terminal half-life of 4.6–5.3 hr [8, 9]; 85% of the administered dose could be recovered in the urine as unchanged species within 24 hr [9]. Major toxic effects in phase I trials consisted primarily of skin toxicity, mucositis and diarrhea [8, 10–14]. Toxic manifestations were not clearly schedule-dependent, although possibly drug-induced neurologic symptoms seemed to occur preferentially with weekly administrations [11]. Of note, there was no clear evidence of consistent myelosuppression in these trials. Hints of activity were found,

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among others, in chondrosarcoma [13] and neurofibrosarcoma [14].

Attractive experimental properties and encouraging therapeutic results in phase I trials prompted us to initiate this phase II study in advanced soft tissue sarcoma. Phase II experience with PALA has slowly accumulated in other tumor types. Some antitumor activity has been detected in malignant melanoma [15, 16], breast cancer [17] and renal cell cancer [18], whereas the single agent activity of PALA has been disappointing in colorectal cancer [19–21], non-small cell lung cancer [22, 23] and bladder cancer [18].

MATERIALS AND METHODS

Thirty-six patients with histologically proven soft tissue sarcoma were treated. All patients had advanced and progressive disease with measurable or evaluable lesions. None of the patients were younger than 15 or older than 75 yr; none had a performance status below 50 on the Karnofsky scale. No chemotherapy had been administered during the 4 weeks prior to entering this trial. Eligibility criteria also included white blood cell counts (WBC) $\geq$ 3000/mm^3, platelet counts $\geq$ 75,000/mm^3, serum creatinine $\leq$ 1.2 mg/dl and normal liver function, unless hepatic impairment could be ascribed to metastatic involvement. Patients with cerebral metastases, intercurrent infection, overt psychosis or marked senility were not eligible.

Five patients were excluded from this analysis because of early death (2), treatment refusal (2) and loss to follow-up (1). Four additional patients were not evaluable because of major protocol violations (2) or inadequate documentation (2). Twenty-seven patients were considered evaluable for therapeutic activity. Fifteen were men, the median age was 55 yr (16–69) and the median performance status on the Karnofsky scale was 80 (50–100) (Table 1). Most evaluable patients had leiomyosarcoma. All had received prior chemotherapy with 1–5 single or multiple drug regimens and 6 had responded to these previous treatments. Fifteen patients had also received prior radiation therapy. Indicator lesions consisted essentially of lung metastases (21) and/or soft tissue lesions (14). Four patients had only abdominal disease to evaluate drug efficacy.

PALA was obtained from the Investigational Drug Branch of the National Cancer Institute, Bethesda, MD. The drug was supplied for i.v. injection in 10-ml ampules containing 100 mg/ml of PALA, sodium hydroxide to adjust to pH 6.5–7.5 acid, and water for injection USP.

Table 1. Pretreatment characteristics in 27 evaluable patients

Men : women	15 : 12
Median age in years	55
(Range)	(16–69)
Median Karnofsky index	80
(Range)	(50–100)
Pathologic subtypes:	
Leiomyosarcoma	8
Liposarcoma	3
Neurofibrosarcoma	3
Synovial cell sarcoma	3
Undifferentiated	3
Fibrosarcoma	2
Rhabdomyosarcoma	1
Others	4
Prior chemotherapy	27
Prior radiotherapy	15

The intact ampules were stored at 2–8°C. PALA was given i.v. at a dose of 2.5 g/m^2 daily for 2 consecutive days and this course was repeated every 2 weeks. The daily dose was diluted in 450 ml saline immediately prior to drug administration and this solution was administered over 60 min. Provisions were made to reduce the dosage if moderate or severe toxicity was encountered. Recovery of major toxic effects was required before retreatment. The study protocol called for dose escalations by increments of 20% if no toxic manifestations were seen in previous courses. Four patients received 2 courses of PALA, 15 received 3 courses and the remaining patients received 5 or more courses. One patient received 17 courses. Initial dosage was reduced in subsequent courses in 4 patients. There were no dose modifications in 11 patients. The remaining patients had dose escalations with or without subsequent de-escalations: seven had one dose escalation, four patients had two and one patient had three. Residual toxicity required postponement of retreatment in 5 courses/4 patients.

Therapeutic responses were classified as follows. Complete remission: disappearance of all symptoms and signs of soft tissue sarcoma for a minimum of 4 weeks; partial remission: significant decrease in size in at least 50% of all lesions for a minimum of 4 weeks, while the remainder are static. In the case of accurately measurable lesions, such a decrease is defined as a reduction by 50% of the product of the two largest perpendicular tumor diameters; stable disease: less than 50% reduction in the product of largest perpendicular diameters of measurable lesions or less than 25% increase in any of the measurable lesions. No appearance of any new lesion; progression: increase of more than

25% in the product of largest perpendicular diameters of any lesion. Also, appearance of any new lesions regardless of a response in other lesions.

RESULTS

Therapeutic responses

One patient with liposarcoma experienced partial remission for 6 weeks from initiation of therapy. This patient was a 69-year-old man with a performance status of 90. He had an easily palpable 9 × 8 cm abdominal mass which had responded to previous combination chemotherapy. Progression of the disease in this patient was noted during withdrawal of PALA because of corneal toxicity. Four patients had stable disease for 12–34 weeks. Twenty-two patients had progressive disease within 4–12 weeks.

Toxicity

All but 2 of the 27 evaluable patients experienced toxic effects. The worst degree of the worst toxic effect was mild in 7 patients, moderate in 11 patients and severe in 7 patients. Skin toxicity was the most frequent side effect (Table 2). Typically, it consisted of an exfoliative dermatitis starting as an erythmatous macular rash involving skin-fold surfaces, the trunk and the face. It occurred in 17 patients and was severe in 4. Fourteen patients had diarrhea (severe and occasionally bloody in 4), 13 had stomatitis (severe in one), 11 had ocular manifestations with conjunctivitis, ulcerous keratitis, and/or photophobia, 6 had mild to moderate nausea and vomiting, and 1 had tingling of the mouth. Questionably drug-related seizures were seen in 2 patients. Toxic effects of PALA generally subsided rapidly and rarely required therapy postponement. Corneal ulcerations were rapidly reversible upon treatment withdrawal, either spontaneously or with 0.1% uridine eye drops. None of the patients experienced myelosuppression. There was no evidence of hepatic toxicity.

Table 2. Toxic effects in 27 evaluable patients

Toxic effect	No. of toxic patients
Dermatitis	17 (4)*
Diarrhea	14 (4)
Stomatitis	13 (1)
Ocular manifestations:	11 (3)
Conjunctivitis	8
and/or Corneal ulcerations	3 (3)
and/or Photophobia	1
Nausea, vomiting	6
Tingling of mouth	1
Seizures	2 ?
Myelosuppression	0

*( ) = No. of patients with severe toxicity.

DISCUSSION

Evaluable patients in this trial represented a favorable population in terms of performance status. However, all had received prior chemotherapy and the probability of obtaining a response with second-line chemotherapy in this refractory disease was minimal. Only one patient achieved a very transient partial response.

The schedule selected for this trial had not been previously tested in phase I trials. Initial dose and dose modifications used in our study seemed, however, adequate. Overall, two-thirds of the patients experienced mild to moderate toxicity. Toxic effects encountered in this study were similar to those seen with other schedules and consisted mainly of mucocutaneous manifestations and diarrhea. The initial dose was generally well tolerated and dose escalations were possible in nearly one-half of the patients. These observations are corroborated by findings in other phase II trials using the same dose schedule [16, 17].

PALA was introduced into clinical trials with great expectations for the treatment of solid tumors. We conclude that, at the dose and schedule used in this trial, PALA has minimal activity in soft tissue sarcoma after prior chemotherapy. Our results do not encourage further evaluation of the drug in this disease, although a higher degree of activity might be observed in a more favorable patient population and, perhaps, in particular histologic subtypes.

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