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N-(Phosphonacetyl)-L-aspartate (PALA) in Advanced Malignant Melanoma: A Phase II Trial of the EORTC Malignant Melanoma Cooperative Group*

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Abstract—*Thirty-nine patients with measurable advanced malignant melanoma were entered in a phase II trial with PALA. Among the 36 evaluable patients there were 18 men and 18 women, with a median age of 53 yr (29–73) and a median performance status (Karnofsky) of 100 (50–100). Indicator lesion consisted essentially of soft tissue lesions (29 patients) and/or lung metastases (9 patients). Only three patients had received prior chemotherapy. PALA was given as a 60-min i.v. infusion at a daily dose of 2.5 g/m² for two consecutive days. Courses were repeated every two weeks. A median number of 3 courses (2–8) were administered. Partial response (> 50%) was obtained in 4 patients for 6–17 weeks. Eight patients had stable disease after 3 courses of PALA and 24 had progressive disease. Toxic effects were generally mild to moderate and mainly included cutaneous toxicity, nausea and vomiting, stomatitis, and diarrhea. Myelosuppression was rare and negligible. It is concluded that PALA given at the dose schedule selected for this trial is fairly well tolerated and has borderline antitumor activity in good-risk patients with advanced malignant melanoma.*

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. Some antitumor activity has been previously detected with PALA in maligant melanoma [15]. This report deals with a cooperative phase II trial of the drug in this disease.

MATERIALS AND METHODS

Thirty-nine eligible patients with histologically proven malignant melanoma were entered

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in the trial. All patients had advanced and progressive disease with measurable lesions. No chemotherapy had been administered during the 4 weeks prior to entering this trial. Eligibility criteria also included age ≤ 75 yr, performance status (Karnofsky) ≥ 50, white blood cell counts (WBC) ≥ 3000/mm^3, platelet counts ≥ 75,000/mm^3 and normal serum creatinine levels. Patients with symptoms and signs of cerebral metastases or intercurrent infection, and patients with overt psychosis or marked senility were not eligible.

Three patients were excluded from this analysis because of inadequate data reporting or treatment discontinuation after a single course of PALA due to rapidly progressive disease. Thirty-six patients were considered evaluable for therapeutic activity (Table 1). Men and women were equally represented, the median age was 53 yr (range 29–73) and the median performance status was 100 (range 50–100). Only three patients had received prior chemotherapy and four had received prior radiation therapy. Indicator lesions consisted essentially of soft tissue lesions (29 patients) and/or lung metastases (9 patients). Liver involvement was the sole indicator lesion in two patients.

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, and water for injection USP. 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 courses were 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. Six patients received 2 courses of PALA, 21 received 3 courses, 8 received 4–6 courses and the remaining patient received 8 courses. Initial dosage was reduced in subsequent courses in 3 patients. There were no dose modifications in 17 patients. The other patients had dose escalations with or without subsequent de-escalations: five had one dose escalation and eleven had two or more dose escalations, with a maximum of five.

Therapeutic responses were classified as *complete response*: disappearance of all symptoms and signs of malignant melanoma for a minimum of 4 weeks; *partial response*: decrease by at least 50% in the sum of the products of the two largest perpendicular tumor diameters of all lesions for a minimum of 4 weeks from initiation of therapy; *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; *progression*: increase of more than 25% in the product of largest perpendicular diameters of any lesion, and also the appearance of any new lesions regardless of a response in other lesions.

Table 1. Pretreatment characteristics in 36 evaluable patients

Men : women	18 : 18
Median age in years	53
Range	(29–73)
Median Karnofsky index	100
Range	(50–100)
Indicator lesions	
Soft tissue	23
Lung	5
Soft tissue and lung	4
Others	4
Prior chemotherapy	3
Prior radiotherapy	4

RESULTS

Therapeutic responses

Four patients with soft tissue lesions experienced partial response for 6, 6+, 14 and 17 weeks from initiation of therapy and eight patients had stable disease after 3 courses (Table 2). One responder and two patients with stable disease underwent surgical removal of their malignant lesions after 3 courses of PALA. Disease progression was noted in the remaining 24 patients.

Table 2. Therapeutic effect of PALA

	No. of patients
Complete response	0
Partial response	4
Stable disease	8
Progression	24

Toxicity

Overall, the treatment was fairly well tolerated. Toxic effects of PALA generally subsided rapidly and, rarely, required therapy postponement. No toxicity was reported in 6

patients. Skin toxicity was the most frequent toxic effect (Table 3). 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 20 patients and was severe in 3. Fourteen patients had nausea and vomiting (severe in one), twelve had stomatitis (severe in one), eleven had diarrhea (severe in two) and three had vaginitis. Other toxic effects consisted of somnolence (one patient), headache and dizziness after a rapid infusion of PALA over 20 min (one patient), proctitis (2 patients), cystitis (one patient), conjunctivitis (one patient) and alopecia (one patient). Mild leukopenia was noted in 2 patients. No other toxic effects were encountered in this trial.

Table 3. Toxic effects in 36 evaluable patients

Toxic effect	No. of toxic patients
Dermatitis	20 (3)*
Nausea, vomiting	14 (1)
Stomatitis	12 (1)
Diarrhea	11 (2)
Vaginitis	3
Myelosuppression	2
Neurologic manifestations	2
Proctitis	2
Cystitis	1
Conjunctivitis	1
Alopecia	1

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

DISCUSSION

Evaluable patients in this trial represented a favorable population in terms of extent of disease and performance status. The vast majority had received no prior chemotherapy. Responses were seen in only 11% of the patients. They always consisted of partial shrinkage of soft tissue lesions and were short-lasting whenever response duration could be evaluated.

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. Most 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 about 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. Its single agent activity has been, however, largely disappointing in soft tissue sarcoma [16], colorectal cancer [18–20], non-small cell lung cancer [21, 22] and bladder cancer [23], whereas initial results in breast cancer [7] and renal cell cancer [23] warrant further consideration. Results of our trial indicate that PALA seems to have borderline activity against advanced malignant melanoma, as already suggested by others [15].

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