Phase II study of perifosine in previously untreated patients with metastatic melanoma

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Summary

Purpose: To assess the response rate and toxicity of the alkylphosphocholine analogue, perifosine, in patients with metastatic or recurrent malignant melanoma.

Patients and Methods: Patients had histologically proven, unidimensionally measurable disease which was incurable by standard therapy. Prior adjuvant immunotherapy was allowed but patients had not received prior chemotherapy. Perifosine was given orally as a loading dose of 900 mg on day 1 followed by a maintenance dose of 150 mg po on days 2–21 in a 28 day cycle. The loading dose was 300 mg on day 1 of all subsequent cycles. Tumour response was assessed every 2 cycles.

Results: 18 patients were accrued over 7 mos. No objective responses occurred in the 14 evaluable patients. Three patients (21%) achieved stable disease after 2 cycles and 11 had progression. Seventeen patients were evaluable for toxicity. Grade 3 or 4 non-hematologic toxicities included: diarrhea (12%), arthralgia (12%), nausea (6%), headache (6%), and fatigue (6%). No grade 3 or 4 hematological or biochemical toxicity were observed. Seventy-seven percent of patients received ≥90% of planned cycle 1 dose intensity and 58% received ≥90% of planned dose for cycle 2+. Four patients required dose reductions; treatment was delayed in 5 patients; and 5 patients missed doses because of toxicity.

Conclusions: Perifosine can be safely administered when given as an initial loading dose followed by daily maintenance therapy over 28 days. Gastrointestinal toxicity is common but generally of low grade. Hematological toxicity is minimal. No objective responses were observed. No further development of single-agent perifosine is recommended in malignant melanoma.

Introduction

The incidence of malignant melanoma has dramatically increased over the past decade. In Canada, this increase in incidence and mortality rate mirrors that in the United States, especially in males. In 2003, it is estimated that approximately 3900 new cases of melanoma will be diagnosed and that over 800 patients will die from this disease [1]. Patients who present with advanced disease, or who relapse after initial treatment for melanoma, have a grim outlook, with a 5-year survival rate of less than 5% [2].

Patients with advanced and/or recurrent disease have few effective treatment options available. Surgical excision of resectable disease remains the mainstay of management in many patients. Cytotoxic chemotherapy, either single agent DTIC or combination regimens, may induce remissions in approximately 20% of patients, but the impact on survival has not yet been demonstrated [3]. Biological agents, such as interferon and interleukin-2, have also been studied in metastatic melanoma and may be associated with durable responses in a small percentage of patients [4, 5]. More recently, biochemotherapy has been evaluated in randomized controlled trials and has not proven to be advantageous over cytotoxics or immunotherapy alone [6]. Overall, the impact of current therapeutic strategies on advanced malignant melanoma
has been modest, and there is a pressing need for the development of new and effective agents for the management of this disease.

Recent observations of the molecular changes associated with melanoma may provide some clues regarding pathways which may be best targeted in the development of new therapeutic strategies. Many labs have found that p16 function is lost in melanoma [7]. This protein plays a key role in inhibiting cell cycle progression at the G1 checkpoint and hence, its loss leads to cell cycle progression and increased proliferation. In some series, p16 loss is associated with higher risk primary lesions and/or is more common in metastatic tissues [8]. Consequently, agents which may block cell cycle at G1 are therefore of particular interest to evaluate in melanoma.

The alkylphosphocholine (APC) analogues, miltefosine and perifosine, interact with cell membranes and interfere with several signal transduction pathways [9, 10]. As a result, MAPK activation is inhibited, the second messenger of IP3 is inhibited, and of relevance in melanoma, perifosine appears to upregulate P21W AK1, which leads to cell cycle arrest at G1/S and G2/M [11].

APC represents a new class of lipid-related compounds that exhibit promising anti-cancer activity and a different spectrum of toxicity than conventional cytotoxic agents [12, 13]. Perifosine (1,1-dimethyl-4[(octadecyloxy)hydroxyphosphinyl]oxy]-piperidinium inner salt) is a synthetic, substituted heterocyclic alkylphospholipid, structurally related to miltefosine [14]. The anti-tumour activity of miltefosine was initially evaluated in the 1980’s but was not developed further because intravenous administration lead to hemolytic anemia, and oral administration caused moderately severe gastrointestinal toxicity [15]. Consequently effective drug levels could not be reached. Perifosine was identified as a potentially active and better tolerated analog of miltefosine [16]. Its spectrum of activity across the NCI 60 cell line screen was very similar to miltefosine. Perifosine has been shown to be more active and better tolerated than miltefosine in non-clinical models. Perifosine exhibited marked activity in animal and human tumour cell lines resistant to standard chemotherapeutic agents with relative sparing of normal cells, including macrophages and bone marrow cells [17].

The activity of perifosine has been evaluated in numerous human and murine cell lines. In vitro, cell lines demonstrating the greatest sensitivity to perifosine included KB (larynx), LNCaP (prostate), MAI-PaCa-2 (pancreas), DLD-1 (colorectal), and SK-HEP-1 (liver). In the SRB/metabolic capacity assay, M14 (melanoma) was amongst the most sensitive cell lines with IC50 values of 0.2–3.1 micrograms/mL [14]. The in vivo activity of perifosine has been evaluated via oral dosing in various schedules in several transplanted tumours, as well as in the dimethylbenzanthracene (DMBA) induced mammary tumour model of the rat [18]. Non-clinical studies of perifosine given as a single oral dose (10 mg/kg), demonstrated near complete absorption, with an absolute bioavailability of 81 and 95% in male and female rats. Effects on the hematopoietic tissue were characterized by an increase in cellularity for the bone marrow and an increased extramedullary hematopoiesis. All toxicities, except those in the male genital tract and eyes, were reversible within 13 weeks. Most significant and not clearly reversible were ophthalmologic lesions, specifically retinal degeneration and cataract formation. Clinical chemistry revealed reversible increases in CK, BUN, SGOT, SGPT, and reversible decrease of red blood cell parameters, total cholesterol, triglycerides, inorganic phosphorus, albumin and protein.

Three phase I trials of perifosine have been completed in Europe and have evaluated weekly and daily dosing, as well as an enteric coated formulation. In study D-21266-3040, 36 patients were treated in sequential dose levels of 100, 200, 350, 450, 600 and 800 mg/week [19]. In study D-21266-3079, 22 patients received perifosine in escalating doses of 50-350 mg daily × 21 days [20]. Fatigue, nausea, vomiting and diarrhea were the most frequent toxicities and the maximum tolerated dose was 200 mg/day. In study D-21266-3087, 8 patients were treated at 200 or 350 mg weekly using an enteric coating formulation; however, the coating did not improve the tolerability and reduced its bioavailability [21].

The Division of Cancer Treatment and Diagnosis, National Cancer Institute, have sponsored two phase I trials of perifosine evaluating a loading dose followed by a daily maintenance dose schedule based upon the improved efficacy in the DMBA-induced rat mammary carcinoma model with this schedule, and upon the clinical PK data which showed a long terminal t1/2 of approximately 100 h. The first trial examined the loading dose on day 1 followed by a maintenance dose schedule for 20 days, in patients with solid tumours repeated every 28 days [22]. Thirty patients have been treated on this study and gastrointestinal toxicities and arthralgias have been dose limiting. The maximum tolerated dose and recommended phase II dose were established as: Cycle 1: 900/150 mg loading/maintenance dose and for ≥ Cycle 2: 300 mg/day 1 loading dose followed by 150 mg days 2–21 repeated every 28 days. No clinical responses were observed. The second NCI sponsored phase I trial evaluated a loading dose given only in Cycle 1, followed by a continuous maintenance dose schedule without a scheduled break [23]. One partial response in a patient with uterine sarcoma has been reported. Seven patients had stable disease lasting ≥ two cycles (renal cell carcinoma −2, sarcoma −2, colon carcinoma −2, ovarian carcinoma −1). The pharmacokinetic analyses from both NCI sponsored studies showed