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Didemnin B in metastatic malignant melanoma: a phase II trial of the Southwest Oncology Group

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Didemnin B is a cyclic peptide isolated from the marine tunicate *Trididemnin cyanophorum*. It is a known potent inhibitor of RNA, DNA and protein synthesis, with activity against the murine B16 melanoma. Fourteen patients with disseminated malignant melanoma were evaluated in a Southwest Oncology Group phase II trial of didemnin B at 4.2 mg/m^2 by 30 min i.v. infusion every 28 days (SWOG-8754). Only patients with no prior chemotherapy were eligible; prior radiation therapy, surgery and at most one prior biologic regimen were allowed. Patients with brain metastasis were eligible only if the disease in the brain had been treated and controlled. All patients had to have normal renal and hepatic function and adequate granulocyte and platelet counts, a performance status of 0–2, and bidimensionally measurable disease. Fourteen patients were entered on the study; five received one and nine received two courses of didemnin B. No responses were noted among the 11 patients evaluable for response. Five patients developed unusual but reversible hypersensitivity reactions during the second course of therapy. Other toxicity in this trial was nausea and vomiting and diarrhea, none of severity greater than grade 3. Given the lack of antitumor efficacy and the unusual toxicity, further evaluation of didemnin B in this dose and schedule in malignant melanoma is not warranted.

Key words: Chemotherapy, didemnin B, melanoma, phase II trial.

Introduction

Malignant melanoma accounts for approximately 1% of all cancer in the US. Once distant metastasis occurs, the outlook is poor, with median survival ranging from 2 to 11 months depending upon the sites of involvement.[1] Chemotherapeutic drugs have had little effect on survival. Response rates for single agents such as DTIC and BCNU vary from 10 to 20%; combination chemotherapy may yield response rates as high as 50%, but has not been shown to be associated with prolonged survival.[2] The Southwest Oncology Group (SWOG), as well as others, has been conducting phase II trials to attempt to identify new agents with activity against metastatic malignant melanoma. One such agent, didemnin B (NSC-325319), is a cyclic depsipeptide isolated from the marine tunicate *Trididemnin cyanophorum*.[3] Didemnin B is the most potent of three related compounds—didemnins A, B and C (named in order of silica gel chromatographic elution)—obtained from this marine organism during a search for new antineoplastic agents.[4] The drug consists of a novel ring peptide structure containing hydroxyisovalerylproprionate and a stereoisomer of the highly unusual amino acid statine (Figure 1). Didemnin B is a potent inhibitor of DNA, RNA and protein synthesis, and has been shown to have activity against the L1210 leukemia *in vitro* as well as the P388 leukemia and B16 melanoma implanted intraperitoneally in mice.[5] In the B16 melanoma model, there did not appear to be a significant schedule dependency.[5] Didemnin B also was found to have significant antitumor activity when tested in the human tumor colony-formation assay during brief (1 h) exposures.[6] Using a 30 min intravenous infusion repeated every 28 days, we

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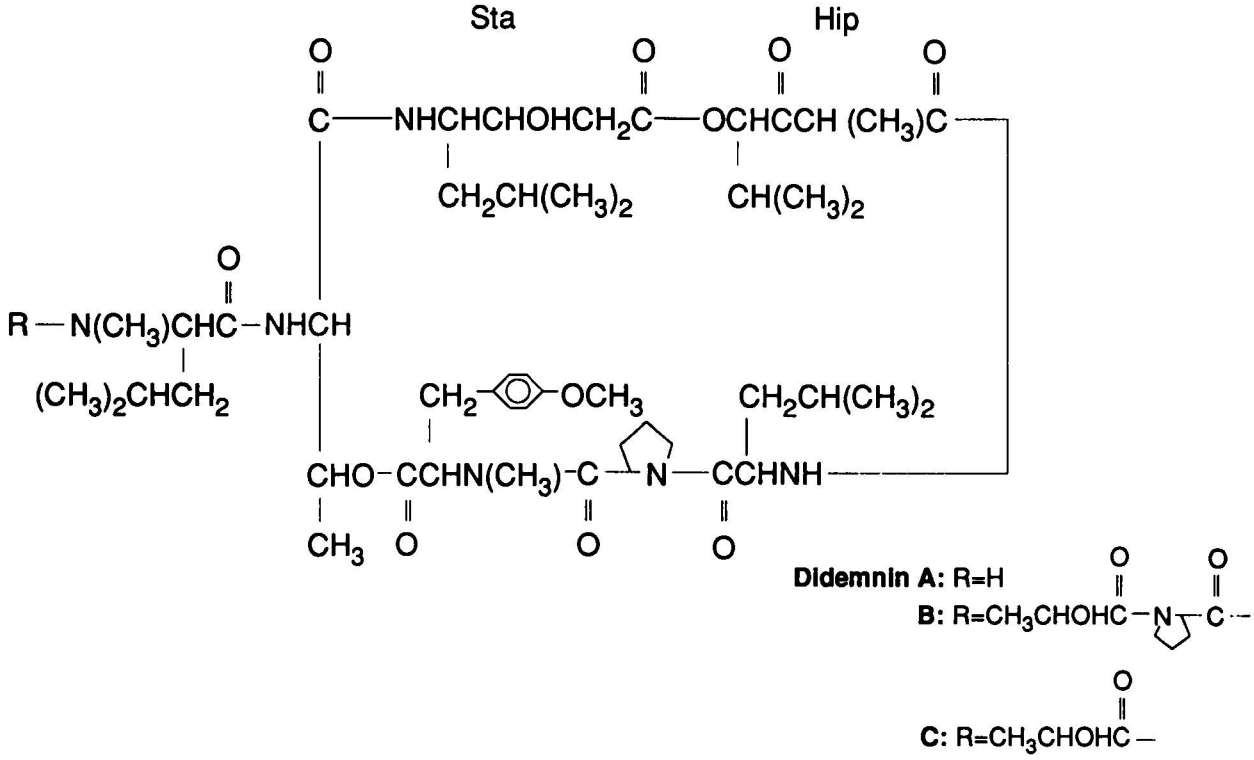

Figure 1. Molecular structure of the didemnins. Didemnins B and C are derivatives of didemnin A, differing only in the structure of a side chain. Sta, statine; Hip, α-(α-hydroxyisovaleryl)propionic acid.

evaluated the effects of didemnin B in patients with metastatic malignant melanoma.

Materials and methods

Patients with a pathologically verified diagnosis of malignant melanoma and distant metastatic disease (AJCC Stage IV) were eligible for this study (SWOG-8754). Only patients with no prior chemotherapy were eligible; prior radiation therapy, surgery and at most one prior biologic regimen were allowed. Twenty-eight days had to have elapsed since completion of radiation therapy and 7 days since surgery for the patient to be treated. Patients with brain metastasis were eligible only if the disease in the brain had been treated and controlled, and there were other sites of evaluable disease. All patients had to have bidimensionally measurable disease, a SWOG performance status of 0–2 and a life expectancy of at least 6 weeks. Pretreatment granulocyte count had to be $\geq 1500/\mu l$ and platelet count $\geq 100\ 000/\mu l$. Patients were also required to have a serum creatinine of ≤ 2.0 mg/dl, serum bilirubin ≤ 1.5 mg/dl and AST (SGOT) ≤ 1.5 times the institutional upper limit of normal. Patients could not receive concomitant radiation therapy, chemotherapy, hormonal therapy, biologic therapy or colony-stimulating factors while on the protocol. Pregnant women were not eligible and patients had to be at least 18 years of age. Pretreatment lab studies, as well as X-rays, ultrasounds and scans used for tumor measurement, had to be obtained within 14 days of patient registration. Institutional Review Board approval and the patient's written informed consent were required prior to the patient's entry into the study.

All patients received an initial dose of didemnin B 4.2 mg/m^2 i.v. in 150 ml of normal saline over 30 min on day 1. All patients were required to receive antiemetic coverage, usually consisting of metoclopramide 1–2 mg/kg i.v., dexamethasone 20 mg i.v. and diphenhydramine 50 mg i.v., prior to and again 1–2 h after the treatment with didemnin B. Patients were to continue therapy until they developed tumor progression or intolerable toxicity, or withdrew at their request. In the absence of any significant toxicity after the first course, the dose was escalated to 4.9 mg/m^2. Dose reductions were required for nausea, vomiting or hepatic toxicity.

The study design called for an initial group of 15 eligible patients whose response to treatment could be evaluated. If one or more of these achieved an

objective response (complete or partial), then 12 additional patients would be entered. Six or more responses among 37 patients, in the absence of prohibitive toxicity, would lead to a recommendation for further evaluation of the agent in melanoma. Using this design, a drug with a true response rate of 10% or less would have a 0.95 probability of being rejected for further evaluation, while a drug with a true response rate of 30% would have an 0.86 probability of being selected for further study.

Results

Fourteen patients (11 males and three females) between the ages of 30 and 77 (median 47) were entered onto the study. Three patients were ineligible due to inadequate baseline documentation of disease which made them non-evaluable for response. All 14 patients, however, received protocol therapy and were evaluable for toxicity. A total of 23 courses of didemnin B were administered. Five patients received one course of the drug; three had disease progression prior to the second course, a fourth died on day 12 (not felt to be drug-related) and the fifth refused further treatment. Nine patients received two courses. Second course doses were reduced to 3.5 mg/m^2 for two patients due to grade 2–3 diarrhea following their initial courses, and escalated to 4.9 mg/m^2 for two others.

Five hypersensitivity toxicities were observed during the second course of didemnin B among the nine patients treated with two courses. This included both patients in whom the dose was escalated to 4.9 mg/m^2, two of five treated at the initial dose of 4.2 mg/m^2 and one of two treated at the reduced dose of 3.5 mg/m^2. Four of the reactions began almost immediately upon infusion of the second course of didemnin B and one began either during or shortly after completion of the infusion. These patients all developed facial flushing, facial and periorbital edema, diaphoresis, chills, and rash. The periorbital edema was severe enough to close the eyes in at least one case. Furthermore, three of the patients experienced cardiac events: hypertension, hypotension and arrhythmia. The patient with arrhythmia had a possible history of rheumatic fever and mitral valve prolapse. The hypersensitivity reactions were treated with vigorous hydration, antihistamines, corticosteroids and oxygen if necessary, and all patients were observed at least overnight to verify complete resolution of symptoms. All reactions resolved without further sequelae and none of the five patients received further treatment with didemnin B.

Nausea and/or vomiting of grades 1–2 occurred in nine patients and diarrhea of grades 2–3 occurred in two. One patient sustained a grade 2 transaminase elevation 8 days after the first dose of didemnin B; however, the relationship of this abnormality to treatment is uncertain since the patient had extensive liver metastases. Coagulation abnormalities and bleeding, observed in preclinical toxicity studies in dogs,[7] was not encountered on this trial.

All eligible patients had distant metastatic disease; sites of disease included lymph nodes beyond the regional node groups (six patients), lung (five), liver (four), and brain, bone, spleen and pleura (one each). Post-treatment disease status was not able to be assessed for three of the 11 eligible patients: one died on day 12 after one dose of didemnin B (death presumed secondary to progressive disease), a second refused further treatment or evaluation after one course and the third was treated off protocol after two courses of didemnin B but before response was assessed. One eligible patient had stable disease and the remaining seven had clearly progressing disease (three of these only received one course of therapy). Based on zero responses among 11 eligible patients, the 95% confidence limits for the response rate is 0–28%. All eligible patients expired within 10 months after entering the study (median 3.4 months).

Due to the high frequency of hypersensitivity reactions in the face of no evidence of antitumor activity, the trial was terminated early with only 11 eligible patients.

Discussion

Didemnin B at this dose and schedule does not appear to be effective in the treatment of metastatic malignant melanoma. Five patients experienced hypersensitivity reactions to the second course of didemnin B, primarily consisting of chills, diaphoresis, facial edema or ruddiness and cardiac events. All patients experiencing toxic reactions had normal liver and renal function at the time of drug administration. With only nine patients receiving a second course of treatment, it was not possible to identify any factors associated with risk of developing hypersensitivity reactions. All the hypersensitivity reactions resolved without sequelae after receiving vigorous hydration, oxygen, and further antihistamines and corticosteroids. These patients were observed overnight at a minimum and appro-

priate adverse drug reaction notifications were filed. Allergic reactions have been noted in other studies utilizing didemnin B.[8–11] The reaction is uncommon with the first dose of didemnin B and has been described most often during the infusion of the second dose.[8] In one other study, two patients were retreated with didemnin B after a prior hypersensitivity reaction without recurrence of symptoms, using prophylactic steroids, diphenhydramine and cimetidine.[9] The hypersensitivity reactions may be due to the 5% polyoxyethylated castor oil vehicle (Cremophor-EL; BASF, Ludwigshaven, Germany), rather than the didemnin B itself.[8] Cremophor-EL, a non-ionic surfactant used as a solubulizer for poorly soluble drugs, has also been implicated as the agent responsible for hypersensitivity reactions to paclitaxel (Taxol),[12] cyclosporine[13] and vitamin K.[14]

Conclusion

Didemnin B at this dose and schedule showed no evidence of antitumor activity against metastatic malignant melanoma, with none of 11 evaluable patients responding and a 3.4 month median survival. Although the early termination of the study precludes ruling out some level of antitumor response, the significant incidence of potentially life-threatening hypersensitivity reactions, combined with the lack of any observed effect in the 11 patients treated, indicates that further studies are not warranted with this agent in melanoma.

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