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Oral vinzolidine as therapy for Kaposi's sarcoma and carcinomas of lung, breast, and colon/rectum

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Summary. *Vinzolidine, a semisynthetic vinca alkaloid, was studied as oral therapy in 30 patients with Kaposi's sarcoma, non-small cell lung cancer, colorectal cancer, and breast cancer. Substantial variations in morbidity were observed among the patients, some patients receiving doses up to 45 mg/m² without toxicity while others had severe hematologic toxicity at doses as low as 25 mg/m². Nausea/vomiting and diarrhea also occurred. Responses were seen in two of 11 patients with Kaposi's sarcoma but not in other patients. Unpredictable severe hematologic toxicity led to early closure of this study. The heterogeneity of patient tolerance may relate to variable oral drug bioavailability, and it is conceivable that vinzolidine could be administered more safely by the IV route.*

Introduction

Vinzolidine (LY 104208), a vinca alkaloid, is a semisynthetic modification of vinblastine. That modification, the incorporation of a heterocyclic oxazolidinedione ring, has produced an agent that is rapidly absorbed [5] when administered PO and has increased lypophilicity compared with vinblastine. Phase-I studies of vinzolidine have revealed primarily hematologic, gastrointestinal, and neurologic toxicity. Hematologic toxicity has been dose-limiting, and hematologic tolerance has varied substantially among patients [2–4]. In vitro studies of vinzolidine's activity have suggested a lack of cross-resistance with vinblastine and have also suggested antineoplastic activity in gastrointestinal, breast, and lung cancers, and in melanoma [1, 6]. Early clinical trials have shown activity of this agent in lymphoma, colon cancer, pancreatic cancer, breast cancer, lung cancer, and Hodgkin's disease [2–4, 7].

In January 1983, we commenced phase-II studies of PO vinzolidine in lung cancer, breast cancer, colon cancer, and Kaposi's sarcoma [in patients with the acquired immunodeficiency syndrome (AIDS)]. While our intention was to study vinzolidine with a patient sample sufficiently large for a reasonable estimate of clinical activity, unexpected hematologic toxicity resulted in the closing of this study to new patient entry in August 1983, prior to full projected patient entry. This paper presents toxicity and efficacy data in the patients entered.

Material and methods

Patients entered on this study met the following criteria: diagnosis of incurable (metastatic, recurrent, or not resectable for cure) Kaposi's sarcoma or carcinoma of the lung (non-small cell), breast, or colon/rectum; active measurable disease; no prior therapy in the preceding 4 weeks and no concomitant chemotherapy, radiation therapy, or immunotherapy; ambulatory status with life expectancy $\geq$ 12 weeks; creatinine $\leq$ 2 mg/dl, bilirubin $\leq$ 2 mg/dl, leukocytes $\geq$ 4,000/mm², granulocytes $\geq$ 1,500/mm³, platelets $\geq$ 100,000/mm³; capability of oral alimentation; and provision of an informed consent. Patients with limited epidermoid carcinoma of the lung had previously failed irradiation. Patients with breast cancer had failed at least two major chemotherapeutic agents and first-line hormonal therapy (or were estrogen receptor-negative). Patients with breast cancer confined to the chest wall had additionally failed irradiation. Patients were excluded in the event of pregnancy, active brain metastases, active infection, or second active malignancy.

Patients were scheduled to receive vinzolidine PO every 2 weeks. The starting dose was 25 mg/m² in patients with Kaposi's sarcoma or patients felt to have impaired bone marrow reserve, and was 30 mg/m² in other patients. Doses were then escalated or reduced on the basis of toxicity. Hematologic toxicity was assessed 9 and 14 days after each dose of therapy or as needed. The criteria for grading hematologic toxicity are shown in Table 1. Additionally, for

Table 1. Hematologic toxicity grading scale

Grading scale	Grade			
	I	II	III	IV
Leukocytes	3,000–3,999/m³	1,500–2,999/m³	1,000–1,499/mm³	< 1,000/mm³
Granuloctes	1,000–1,499/mm³	750–999/mm³	500–749/mm³	< 500/mm³
Platelets	100,000–150,000/mm³	50–99,999/mmm³	25,000–49,999/mm³	< 25,000m ³

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other severe or intolerable toxicity, therapy was delayed by 1 week or until toxicity abated and was then restarted at a dose decreased by 10 mg/m^2. If severe toxicity occurred despite two such dose decrements, or if life-threatening toxicity occurred, treatment was stopped (Table 2).

Patients continued with the therapy until disease progression, unacceptable toxicity, or patient withdrawal from the study. Patients were considered evaluable for toxicity after receiving a single dose of therapy and evaluable for efficacy after receiving either a single dose of therapy which resulted in ≥ grade-I hematologic toxicity or two doses of therapy regardless of toxicity. Complete response (CR) was defined as disappearance of all measurable and evaluable disease for ≥ 4 weeks. Partial response (PR) was defined as a ≥ 50% decrease in the sum of the products of the diameters of all measurable lesions lasting ≥ 4 weeks. In the case of malignant hepatomegaly, the sum of the distances of hepatic extension below the costal margin at the midclavicular lines and xiphoid process was used instead of the product of the diameters. If any lesions increased in size or new lesions appeared this precluded inclusion in the CR or PR group. Minimal response was defined as unequivocal objective tumor shrinkage lasting ≥ 4 weeks but not meeting the criteria of a PR or CR; again any new lesions or size increases of existing lesions precluded inclusion in this group. Progression was defined as the appearance of new lesions or a ≥ 25% increase in the sum of the product of diameters of measurable lesions (hepatomegaly scored as above) or tumor-induced death. All other responses were classed as stable disease.

Results

Patients entered

Thirty patients were entered on study. They are profiled in Table 3. One additional patient with colon cancer had vinzolidine prescribed but developed a bowel obstruction from abdominal carcinomatosis and did not successfully ingest his pills due to emeses. He was subsequently treated for his obstruction surgically and had no known toxicity from any absorbed vinzolidine. Nineteen patients, including all 12 with Kaposi's sarcoma, were started at a 25-mg/m^2 dose. The 11 other patients were started at a 30-mg/m^2 dose.

Doses delivered

Patients received a median of two doses of therapy (range 1–10, mean 3.4). All patients were evaluable for toxicity, and 29 of 30 patients were evaluable for efficacy. The condition of the patient not evaluable for efficacy had been initially diagnosed as Kaposi's sarcoma but was later reclassified as lymphadenopathy syndrome.

Dose adjustment

Dose escalation to above the starting dose occurred a total of 29 times in 19 patients, including 11 of 19 patients started at 25 mg/m^2 and eight of 11 started at 30 mg/m^2. The maximum dose level reached was 45 mg/m^2. In 16 patients, dose escalation was limited by toxicity, whereas in the remaining patients dose escalation was limited because the patients withdrew from the study. Dose reductions occurred following the starting dose in four patients (3 at 25 mg/m^2). An additional three patients (all at 25 mg/m^2) had toxicity that would have required dose reduction but did not receive a second dose of therapy.

Toxicity

Dose-limiting toxicity was hematologic and gastrointestinal. Five patients developed grade-IV granulocytopenia: three at a starting dose of 25 mg/m^2, one at a starting dose of 30 mg/m^2, and one after escalation from 30 mg/m^2 (which was associated with no hematologic toxicity) to 35 mg/m^2. Nadir granulocyte counts in these patients were 0, 0, 78, 150, and 494

Table 2. Therapy adjustment

Grade of day−10 toxicity		Grade of day−15 toxicity	
III or IV	or	III or IV	Decrease 10 mg/m^2, restart when WBC > 3,900/mm^3 and platelets ≥ 100,000/mm^3
II	or	I or II	No change in dose, treat when WBC ≥ 3,900/mm^3 and platelets ≥ 100,000/mm^3
0 or I	or	0	Increase by 5 mg/m^2, treat on day 15

Table 3. Patients treated with vinzolidine (30)

Diagnosis	No. of Pts	Age Median (range)	Sex (M/F)	Past treatment	Sites of disease
Kaposi's sarcoma	12[a]	33 (23–44)	12/0	11 none; 1 RT and CT[b]	Skin 11
Colorectal carcinoma	8	59 (32–69)	5/3	7 CT; 1 CT and RT	Liver 7, lung 3, soft tissue/lymph nodes 4, bone 1
Lung carcinoma (non-small cell)	5	60 (44–73)	2/3	2 CT and RT; 2 CT; 1 RT	lung 5, soft tissue/lymph nodes 1, bone 1
Breast carcinoma	5	59 (50–63)	0/5	5 CT and RT	Bone 4, liver 3, chest wall 2, lung 1

[a] One patient whose condition was initially diagnosed as lymphadenopathic Kaposi's sarcona was later felt on pathologic review to have lymphadenopathy syndrome without Kaposi's sarcoma

[b] RT, radiation therapy; CT, chemotherapy

granulocytes/mm^3. Of the five patients with grade-IV granulocytopenia, one had colon cancer, two had breast cancer, and two had Kaposi's sarcoma/AIDS. One of the two patients with Kaposi's sarcoma and grade-IV granulocytopenia acquired *Pneumocystis carinii* pneumonia, and died 15 days after a single dose of vinzolidine. Grade-III granulocytopenia was seen in two additional patients (breast and lung cancer). Each episode occurred after a single dose escalation to 30 mg/m^2 and 35 mg/m^2. Two of the patients with grade-IV granulocytopenia also had significant (grade-III and grade-IV) thrombocytopenia. For 10 patients, however, no hematologic toxicity was noted at any time during the study. There was no clear relationship between the existence of hematologic toxicity and age, diagnosis, past therapy, liver function, or sites of disease.

Gastrointestinal toxicity also occurred. Moderate to severe diarrhea was seen in five patients and moderate to severe nausea/vomiting was seen in two patients. Three patients had mild elevation of SGOT. No nephrotoxicity, neurologic toxicity, or stomatitis was seen. Malaise was common.

Response to therapy

Partial responses lasting 11 and 12+ weeks were seen in two of 11 patients with Kaposi's sarcoma evaluable for response. These patients were both treated at 25 mg/m^2 every 2 weeks without dose escalation. One additional patient achieved a minimal response lasting 8 weeks. One patient withdrew from the study with stable disease at 7 weeks. The one patient who died of *Pneumocystis carinii* pneumonia had stable disease at the time of death. All other patients had progressive disease.

No responses were seen in the patients with colorectal carcinoma, lung cancer, or breast cancer.

Discussion

Vinzolidine is a new vinca alkaloid, which appeared worth investigating on the basis of PO absorption [5], possible non-cross-resistance with other vinca alkaloids [1, 6, 7] and preliminary evidence of activity in tumor types, such as colon cancer, that are not commonly responsive to other vinca alkaloids [2–4, 7]. It seemed of particular interest in Kaposi's sarcoma, in which other plant alkaloids (vinblastine, etoposide) have known activity.

Pharmacokinetic studies have suggested a long terminal half-life (35–100 h) [3, 5], which supports a schedule based on intermittent (e.g., every 2 weeks) doses of therapy. Phase-I studies had suggested starting doses of 30–35 mg/m^2 [2] or of 55 mg/m^2 [3] on an every 2-weeks schedule, and had suggested substantial variability in dose-dependent toxicity from patient to patient. Tolerable weekly doses were reported to range from 20 mg/m^2 to 70 mg/m^2 [4].

Our data confirm a substantial heterogeneity in patient tolerance of vinzolidine, as some patients had severe hematologic toxicity at a dose of 25 mg/m^2 while in others the dose was escalated to 45 mg/m^2 without toxicity. Hematologic intolerance did not seem related to diagnosis, although patients with Kaposi's sarcoma might have been expected to be at increased risk of marrow suppression due to their known propensity for spontaneous pancytopenia and poor tolerance of myelotoxic therapy. The occurrence of *Pneumocystis carinii* pneumonia in the patient with AIDS and Kaposi's sarcoma may reflect the immunosuppressive and myelotoxic effects of therapy in that setting.

Gastrointestinal toxicity (like hematologic toxicity) varied substantially from patient to patient. Suprisingly, neurotoxicity was not seen. This may be related to infrequent long-term vinzolidine therapy (6 patients received > 4 doses) and perhaps to a relative paucity of patients with prior vinca alkaloid therapy (7 of 30 patients receiving a median of 3 doses).

Our study did not assess the absorption rate, bioavailability, or metabolism of vinzolidine, but it is possible that variability among patients as to hematologic and gastrointestinal tolerance of this drug is in part related to such pharmacologic factors. In designing this study we attempted to deal with that possibility by starting patients at what was considered to be a quite safe starting dose, and then gradually escalating patient dosage as tolerated. This strategy was not effective, largely because we saw significant excessive hematologic toxicity at our starting dose and because, at least in one patient, lack of hematologic toxicity at the starting dose did not predict safety at a dose 5 mg/m^2 (17%) higher. While it is conceivable that PO vinzolidine might be used safely if the starting dose was substantially lower (e.g., 10 mg/m^2) and was escalated as tolerated, such an approach might result in the achievement of ineffective dose levels (with a theoretical risk of inducing drug resistance) in the majority of patients. Because of these considerations, this study was terminated prior to collection of sufficient numbers of patients for a reasonable assessment of drug efficacy.

In the patients who were studied, activity of drug was seen (at a low level) in Kaposi's sarcoma but was not seen in colorectal, breast, or long cancers. The small sample size precludes meaningful conclusions, however, and it is possible that in patients who did not experience any drug toxicity the preparation was in fact underdosed.

On the basis of the breadth of the data available regarding vinzolidine, it seems reasonable to pursue studies of its efficacy, but perhaps by the IV route to standardize bioavailability, and with close attention to possible relationships between drug metabolism and drug toxicity. An IV formulation of vinzolidine has ben developed and is scheduled for preliminary evaluation (R. Nelson, personal communication).

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