Phase I trial of vinorelbine and diphenylhydantoin in patients with refractory carcinoma

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Summary
The anti-epileptic diphenylhydantoin (DPH; Dilantin®) selectively enhances the in vitro cytotoxicity of vinca microtubule poisons in both parent sensitive and multi-drug resistant (MDR) human tumor cells. The in vivo clinical activity of this combination has not been fully evaluated. Purpose: To determine the maximum tolerated dose (MTD), dose-limiting toxicities, and preliminary antitumor activity of the combination of intravenous (IV) bolus vinorelbine (VRL) and oral diphenylhydantoin (DPH) in patients (pts) with refractory solid tumors. Methods: Cohorts of 3–6 pts with refractory cancer were treated with escalating doses of weekly IV bolus VRL (I –20.0 mg/m²; II –22.5 mg/m²; III –25.0 mg/m²; IV –27.5 mg/m²; V –30.0 mg/m²; VI –32.5 mg/m²) combined with a fixed oral dose of DPH (400 mg/day) until MTD or progression. During each 35 day cycle, pts received DPH 400 mg/day administered orally on Days −6 to Day +22 and weekly IV bolus infusion of VRL on Days +1, +8, +15, and +22. The cohort treated at the MTD was expanded to further define toxicity. Results: A total of 25 evaluable pts. (9 men; 16 women) were treated with VRL and DPH at dose levels I (n = 5), II (n = 3), III (n = 2), IV (n = 3), V (n = 7) and VI (n = 5) in 5 week cycles over a 16 month period. Dose limiting toxicity occurred at dose level VI (VRL 32.5 mg/m²) and included grade 3 leukenopia (n = 2), grade 3 neutropenia (n = 1) and grade 4 neutropenia (n = 1) occurring within the first cycle of treatment. There were no responses, however 9 pts had stable disease of variable duration (8–56 weeks) and received a median of 2 cycles of treatment (range 2–14). Conclusion: Intravenous bolus administration of VRL and oral administration of a fixed dose of DPH was well tolerated according to the schedule reported here. Although there were no responses, several patients had prolonged disease stabilization. The recommended phase II dose of VRL when used in this combination is 30 mg/m².

Introduction
Resistance to cancer chemotherapy is a significant problem and may prevent further therapeutic advances in the management of human solid tumors. The vinca alkaloids are widely used in the treatment of a spectrum of human malignancies. Similar to other antitumor agents, tumor cell resistance to vinca alkaloids limit their clinical efficacy. Although multiple mechanisms may be involved (i.e. alteration in cell-cycle checkpoint control and apoptosis), the intrinsic resistance of some solid tumors to cytotoxic therapy may be related to multidrug resistance (MDR) regulated by the energy-dependent P-glycoprotein (p-170) drug efflux pump encoded by the MDR-1 gene [1–4]. Resistance to vinca alkaloids is thought to be mediated by MDR and mutations in α- or β-tubulin that limit drug binding [2, 5]. Vinorelbine (VRL) is a semi-synthetic vinca alkaloid differing from earlier vinca alkaloids by a substitution
at a dosage of 30 mg/m², administered weekly as a single agent or in combination chemotherapy, have been conducted since 1985. Results suggest that VRL has high activity in non-small cell lung cancer (overall response rate of 33–65%), breast cancer (overall response rate of 46–78%) and cisplatin-resistant ovarian carcinoma (overall response rate of 16–35%) [12]. The use of VRL in refractory malignancies has produced variable results with many patients achieving stable disease [13–19].

A variety of MDR modulators have been used in combination with cytotoxic therapy with improved in vitro activity [20]. The anticonvulsant diphenylhydantoin (DPH) has been shown in a selective fashion to potentiate \( p < 0.001 \) the cytotoxic effects of microtubule poisons and is greater \( p < 0.05 \) for agents which depolymerize rather than promote polymerization of tubulin [21]. The modulating effects of DPH are novel with activity even in tumors with the MDR phenotype and the ability to potentiate cytotoxicity at concentrations attainable clinically \( (7.5–20 \, \mu g/ml) \). DPH has enhanced vinblastine (VBL) cytotoxicity in vitro in both wild-type and MDR cancer cell lines [22]. In our laboratory, addition of DPH to varying concentrations of VRL increased by at least 10-fold the cytotoxicity of VRL on HL-60, L1210S and L1210R cell lines in vitro. In a Phase I trial in patients with refractory solid tumors, concentrations of VBL and DPH with significant cytotoxicity in vitro, were well tolerated [23]. Whether the combination of VRL and DPH will be both efficacious and tolerable in patients with refractory carcinoma is unknown.

We conducted an in vitro study followed by a Phase I trial in patients with refractory carcinoma to determine: (1) the in vitro ability of DPH to potentiate the cytotoxicity of VRL in MDR cancer cell lines; and, in a Phase I trial, the (2) maximum tolerated dose (MTD) of VRL when given with a fixed dose of oral DPH, (3) toxicity associated with the administration of VRL by a weekly bolus injection when given with oral DPH, and (4) preliminary objective response secondary to VRL and DPH administration.

**Patients and methods**

**Patients**

Patients with histologically proven metastatic or surgically unresectable solid tumors who have failed conventional therapy or for whom no standard therapy exists were eligible for enrollment. All patients were between 18 and 65 years of age; had bi-dimensionally measurable or evaluable disease; had a life expectancy of ≥3 months; had a performance status (ECOG) of ≤2; had complete recovery from toxicity related to prior hormonal, radiation, or biologic therapy; had pretreatment laboratory values above stated minimum values \( (WBC \geq 3.0 \times 10^9/L, \text{ANC} \geq 1.5 \times 10^9/L, \text{platelets} \geq 100 \times 10^9/L, \text{hemoglobin} \geq 9.0 \text{gm/dl}, \text{serum creatinine} \leq 1.8 \text{mg/dl}, \text{and bilirubin (total)} \leq 1.5 \text{ml/dl}) \); had absence of significant effusions or ascites; had no major surgery requiring general anesthesia within the preceding 28 days; and, had received \( \leq 2 \) prior systemic regimens. Informed consent was obtained from all patients in accordance with Cleveland Clinic and FDA guidelines.

Exclusion criteria included history or evidence of cardiac arrhythmia or congestive heart failure (New York Heart Association Class III or IV); women of childbearing age unless surgically sterile or using effective contraception; pregnant or lactating women; known CNS metastasis as determined by imaging studies \( (\text{i.e. CT scan of brain}) \) or neurological exam; or history of a seizure disorder. In addition, patients were ineligible if they had a history of another malignancy within the past 3 years excluding basal cell carcinoma of the skin or carcinoma in-situ of the uterine cervix; had organ allografts; required ongoing therapy with DPH; required concomitant therapy with agents known to modulate MDR \( (\text{i.e. phe-nothiazines, cyclosporin A, tamoxifen, progesterone, verapamil and quinidine}) \); required ongoing therapy with agents known to modify DPH pharmacokinetics \( (\text{i.e. antacids, sucralfate, theophylline, heparin, nonsteroidal anti-inflammatory agents, corticosteroids, coumadin, allopurinol, omeprazole, and H2-blockers}) \); had received chemotherapy, immunotherapy and/or...