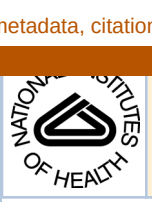

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A phase I evaluation of the combination of vinflunine and erlotinib in patients with refractory solid tumors

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Summary

Purpose—Epidermal growth factor receptor (EGFR) inhibition may overcome chemotherapy resistance by inhibiting important anti-apoptotic signals that are constitutively activated by an overstimulated EGFR pathway.

Methods—This phase I dose escalation trial assessed the safety and efficacy of vinflunine, a novel vinca alkaloid microtubule inhibitor, with erlotinib, an EGFR tyrosine kinase inhibitor, in patients with refractory solid tumors.

Results—Seventeen patients were treated, 10 with continuous erlotinib, and 7 with intermittent erlotinib. At dose level 1, vinflunine 280 mg/m^2 IV day 1 and erlotinib 75 mg PO days 2–21 ("continuous erlotinib") in 21 day cycles, two of four patients experienced DLTs. At dose level -1 (vinflunine 250 mg/m^2 every 21 days and erlotinib 75 mg/day), two of six patients experienced DLTs. The study was amended to enroll to "intermittent erlotinib" dosing: vinflunine day 1 and erlotinib days 2–15 of a 21 day cycle. Two of seven experienced DLTs and the study was terminated. One patient with breast cancer had a partial response; three had stable disease ≥6 cycles. All were treated in the continuous erlotinib group.

Conclusions—Given the marked toxicity in our patient population, the combination of vinflunine and erlotinib cannot be recommended for further study with these dosing schemas.

Keywords

Influnine; Erlotinib; Phase I; Safety and toxicity

Introduction

Vinflunine is a novel, semi-synthetic vinca alkaloid with broad preclinical antitumor activity [1]. Like other vincas, vinflunine exerts its antineoplastic effect through interference with microtubule formation and function, leading to cell cycle arrest at G2/M, and subsequent apoptosis. In contrast to other vincas, vinflunine has a lower affinity for tubulin—a characteristic postulated to reduce neurotoxicity [2].

Single agent phase I experiences identified vinflunine 350 mg/m^2 IV every 21 days as the maximum tolerated dose (MTD) [3]. Due to an excessive rate of hematologic toxicity in early phase II trials, doses in the phase II and III studies were 320 mg/m^2 every 21 days [4]. Common grade 3/4 adverse effects of vinflunine include neutropenia, constipation, and fatigue [2].

Clinically relevant activity of single agent vinflunine has been seen in platinum-refractory bladder cancer [5], anthracycline and taxane pre-treated metastatic breast cancer (MBC) [6], second-line therapy of non small cell lung cancer (NSCLC) [7], and malignant pleural mesothelioma [8], and vinflunine is now being evaluated in combinations in these diseases [2].

Epidermal growth factor receptor (EGFR) is over-expressed in many solid tumors, including those in which vinflunine has demonstrated activity. Furthermore, treatment with vinca alkaloids increases the number of EGFRs on cancer cells in vitro [9,10]. Inhibition of the epidermal growth factor pathway is known to sensitize tumors to chemotherapy, particularly evident in colorectal cancer where treatment with cetuximab and irinotecan can overcome irinotecan resistance [11]. EGFR inhibition may overcome chemotherapy resistance by inhibiting important anti-apoptotic signals that are constitutively activated by an overstimulated EGFR pathway, thus lowering the apoptotic threshold [12].

Erlotinib, an oral tyrosine kinase inhibitor (TKI) of EGFR approved for use in NSCLC and pancreas cancer, inhibits the intracellular phosphorylation of tyrosine kinase [13]. Adverse effects include fatigue, rash, diarrhea, anorexia, and mild dyspnea [13]. The differing adverse effect profiles between erlotinib and vinflunine, potential for synergistic activity, and anticipated activity in a number of tumor types made this an attractive combination. Additionally, synergy between vincas and other HER family members has been demonstrated, specifically in MBC with vinorelbine and trastuzumab (erb2/Her2 antibody) [14].

We undertook a phase I investigation of vinflunine and erlotinib in combination in patients with refractory solid tumors to determine the MTD and recommended phase II dose for future studies.

Patients and methods

Eligibility

Patients had histologically confirmed advanced solid tumors refractory to standard therapies, or for which no standard therapy exists. Other eligibility criteria included: age ≥18 years; >3 month life expectancy; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST); at least 4 weeks post chemotherapy, investigational agent, or surgery; and adequate organ function (bilirubin ≤1.5 mg/dL; transaminases ≤3 times upper limit of normal (ULN), or ≤5 times ULN if known liver metastasis; creatinine clearance ≥60 mL/min by Cockcroft-Gault; platelets ≥100,000/μL; absolute neutrophil count (ANC) ≥1,500/μL). Patients with brain metastases were permitted only if they had undergone CNS directed therapy at least 3 months earlier and had both clinically and radiographically stable disease for at least 8 weeks. Medications known to induce or inhibit cytochrome P450 3A4 (CYP3A4) were discontinued or required to be stable doses for a minimum of 2 weeks prior to enrollment; strong inhibitors (e.g. ketoconazole) and enzyme-inducing antiepileptic drugs (e.g. phenytoin) were not permitted. Other exclusion criteria included: prior allergic reaction to a vinca alkaloid; New York Heart Association class III/IV heart failure, unstable angina, myocardial infarction within 6 months; poorly controlled hypertension; uncontrolled infection or severe illness; and pregnancy, refusal to use contraception, or breastfeeding.

Written informed consent was obtained prior to treatment or any study related procedures. This study was approved by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill.

Dosing and trial design

A standard 3-patient cohort dose escalation scheme was employed, whereby three patients began treatment at dose level 1. If no dose limiting toxicities (DLTs) were observed after completion of the 21 day cycle, three patients were enrolled at the next dose level. However, if one patient developed a DLT, three additional patients were enrolled at that dose level, and if none of these developed a DLT (1 of 6 with DLT), enrollment proceeded at the next dose level. If a second patient (2 or more of 6) experienced a DLT, that dose exceeded the MTD and the dose recommended for phase II trials, defined as the dose level below that which induced DLT in one third or more of patients.

Dose level 1 was vinflunine 280 mg/m^2 IV day 1 and erlotinib 75 mg PO days 2–21 (“continuous erlotinib”). MTD was exceeded therefore enrollment continued with a prespecified dose level -1 (vinflunine 250 mg/m^2 and erlotinib 75 mg/day). Because MTD was again exceeded, the study was amended to enroll patients to a new dose escalation scheme: vinflunine 280 mg/m^2 on day 1 and erlotinib 75 mg/day on days 2–15 of a 21 day

cycle ("intermittent erlotinib"). This regimen was based on data suggesting EGFR TKIs may inhibit G1 cell cycle arrest, thus negating the M-phase effect of vinflunine, while evidence was emerging supporting "pulse" TKI regimens to overcome such effects [15–17].

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (NCI CTCAE v3) [18]. DLTs were defined as any of the following that occurred during cycle 1: any ≥ grade 3 non-hematologic toxicity except fatigue or constipation; ≥ grade 3 constipation lasting ≥ 7 days despite supportive management; grade 3 rash unresponsive to supportive management; grade 4 fatigue; ANC $<0.5 \times 10^9$ cells/L lasting >5 days or associated with fever or infection; or platelet $<25 \times 10^9$ cells/L of any duration or $<50 \times 10^9$ cells/L with major bleeding. Toxicity was assessed weekly during cycle 1 and every 3 weeks for subsequent cycles.

Tumor response was assessed according to RECIST criteria every two cycles with computed tomography (CT) or magnetic resonance imaging scans (MRI) [19].

Midazolam probe for CYP3A4

Vinflunine and erlotinib are both CYP3A4 substrates. Given the known interperson heterogeneity of CYP3A4 activity, we sought to investigate the relationship between CYP3A4 phenotype and toxicity from this combination. CYP3A4 phenotyping has predicted toxicity with other chemotherapeutics [20]. Clearance of midazolam, a CYP3A4 substrate, was used as a surrogate for CYP3A4 activity. Midazolam 1 mg was bolused immediately following vinflunine in the first seven patients. Thereafter midazolam was administered 3 h before vinflunine. Venous blood samples were collected prior to and at 5 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, and 8 h after the end of the midazolam infusion. Samples were collected in EDTA tubes, centrifuged to separate plasma, and stored at−80°C until analysis. Sampling was performed for vinflunine PK analysis, however due to processing errors, the samples could not be reliably evaluated.

Plasma concentrations of midazolam were determined using a modified, validated reverse-phase HPLC method with mass spectrometric detection [21]. Individual midazolam plasma concentrations were used to estimate PK parameters using WinNonlin 4.0 (Pharsight Corp., Mountain View, CA).

Drug administration

Vinflunine was given day 1 of every 21 day cycle as an IV infusion over 20 min with an infusion of 500 mL of 0.9% normal saline. Ondansetron 24 mg PO was given 30–60 min before vinflunine. Erlotinib was started day 2 of each cycle and continued until day 21 in the continuous dosing group and until day 15 in the intermittent group taken 1 h before or 2 h after meals.

Patients who experienced a DLT during cycle 1 underwent a dose reduction of vinflunine only for subsequent cycles. Grade 3 or 4 non-hematologic toxicity and grade 4 hematologic toxicity in subsequent cycles resulted in a 25% dose reduction of vinflunine. Erlotinib dose was decreased to the next level only for grade 3 rash (e.g. from 75 mg to 50 mg). Patients continued treatment until progressive disease, excessive toxicity, or patient preference.

Results

Patient characteristics

Seventeen patients (ten continuous erlotinib, seven intermittent erlotinib) were treated at a single institution between October 2006 and March 2008. All patients received at least one

dose of vinflunine and are included in the toxicity assessment. The median age was 59 years (range 40 to 81), with 8 men and 9 women (Table 1). Most patients received prior chemotherapy, with a median of three prior treatments for metastatic disease.

Dose limiting toxicity and adverse events

In the continuous erlotinib cohorts, 60 cycles of therapy were delivered, with a median of 5 cycles per patient (range 1–13). DLTs observed at continuous dose level 1 (two of four patients) were unstable angina in a patient with known coronary artery disease, and grade 3 asthenia and mouth pain (Table 2). The other two patients continued for 3 and 13 cycles, respectively. The unstable angina event occurred on cycle 1 day 1, prior to the first dose of erlotinib, and was managed medically; he was considered not evaluable due to the use of the study drug vinflunine. DLTs on dose level -1 (two of six patients) were grade 3 nausea and vomiting (despite adequate symptomatic treatment) in one patient, and grade 4 neutropenia lasting longer than 5 days with grade 3 fatigue in another.

In the intermittent erlotinib cohorts, 16 cycles were delivered, with a median of two cycles per patient (range 1–5). One DLT occurred in the first six patients at dose level 1 (grade 3 dehydration and mouth pain, grade 4 abdominal pain and fatigue). To ensure safety, this cohort was expanded. The next patient enrolled experienced DLT (grade 3 dehydration and mouth pain, grade 4 myalgias) for DLT in two of seven patients leading to study termination.

The most frequent adverse events (all grades and regardless of attribution) observed were leucopenia (n=13), neutropenia (n=11), nausea (n=8), vomiting (n=8), and fatigue (n=7) (Table 3). Treatment-related grade 3–4 toxicities were leukopenia, neutropenia, anemia, fatigue, hypokalemia, abdominal pain, and myalgias. These toxicities did not appear to be dose or schedule related.

Of the seven patients who received more than one cycle of vinflunine with continuous erlotinib, five had grade 3 or 4 toxicity. These were predominantly bone marrow suppression, including grade 4 neutropenia in three patients. Of the six patients that received more than one cycle of intermittent erlotinib, two had grade 3 or 4 toxicities.

Constipation and sensory and motor neuropathy, which are common toxicities of vinka alkaloids, were uncommon occurrences in this trial, affecting 24% and 19% of patients respectively, all of which were grade 2 or less.

Clinical benefit

Three patients in the continuous erlotinib cohorts withdrew following DLTs, and one patient in the intermittent arm withdrew to have a lung lobectomy for a stable lung nodule following cycle one. These four were not evaluable for clinical response.

In the continuous dosing cohort at dose level 1, one patient with MBC had a partial response lasting 13 weeks. Five patients had stable disease (range 3–19 weeks). Prolonged stable disease (≥6 cycles) occurred in three patients: a patient with adenoid cystic carcinoma who withdrew for symptomatic deterioration without radiographic evidence of progression after 13 cycles, and two patients with parotid carcinoma treated with 9 and 11 cycles respectively. One patient had primary progressive disease.

In the intermittent dosing cohort, one patient with colon cancer had stable disease for five cycles. The other five patients had primary progressive disease, including one patient with symptomatic brain metastases.

CYP3A4 phenotyping

Midazolam probe PK was performed for CYP3A4 activity in the first ten patients. In an exploratory analysis of the association between midazolam clearance and toxicity, ANC nadir correlated with rate of clearance such that those patients with slower clearance had a lower ANC nadir (Spearman's correlation coefficient 0.49).

Discussion

In this phase I study of vinflunine and erlotinib in combination, the MTD was exceeded even at dose level -1 in which vinflunine was given at 75% and daily erlotinib at 50% of the commonly used anti-tumor doses. MTD was also exceeded in the first dose cohort of vinflunine with intermittently dosed erlotinib. Given the marked toxicity in our patient population, this combination cannot be recommended for further study with these dosing schemas, though several patients had prolonged periods of stable disease including one with MBC and three with head and neck cancers. Another recent study combining a vinca alkaloid with an EGFR inhibitor also demonstrated unacceptable toxicity [22], whereas gefitinib ± vinorelbine in a Chinese population had minimal toxicity and the combination demonstrated improved progression free survival [23].

The extent of toxicity observed was not anticipated. Though limited by small sample size, we explored several variables thought to contribute to chemotherapy toxicity: neither age, nor gender, nor extent of prior therapy appeared related to toxicity. The toxicity may be in part explained by drug interaction of these CYP3A4 substrates. However, administering erlotinib intermittently to avoid competitive CYP3A4 inhibition did not mitigate the toxicity. Unfortunately, samples collected to measure vinflunine pharmacokinetics could not be processed, and thus we cannot comment on whether our patients had higher than expected vinflunine exposure as would be expected if toxicity resulted from an erolotinib-vinflunine interaction.

To date, vinflunine has demonstrated single agent activity in pretreated NSCLC, bladder, and MBC, and combination therapies are being further evaluated in these first line settings [2]. A phase III study of vinflunine versus best supportive care in second line transitional cell carcinoma of the urothelium demonstrated no survival benefit by intention to treat, but a statistically significant 2 month benefit in the eligible population [24]. Other combination studies with vinflunine have been reported using both conventional chemotherapeutics and targeted therapies. Our phase I trial of pemetrexed and vinflunine demonstrated that this combination is safe, and two patients had prolonged stable disease (lung and breast cancer) [25]. Phase II combination studies are in progress. In second-line NSCLC, vinflunine with cetuximab produced partial responses in three of 13 patients and stable disease in five patients [26]. Other studies evaluating TKIs and vinflunine have not been reported.

This phase I study demonstrated that combination vinflunine and erlotinib in continuous or intermittent dosing schedules is poorly tolerated. Other combination therapy trials could investigate alternate dosing regimens and avoid CYP3A4 substrates or inhibitors/inducers.

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Table 1

Patient characteristics

Number treated patients (#)	17
Age, median (range)	59 (40–81)
Tumor Type, n	
Breast	6
Colorectal	3
Adenoid cystic carcinoma of head and neck	2
Parotid (1 adenocarcinoma, 1 squamous cell carcinoma)	2
Lung (adenocarcinoma)	1
Esophageal (squamous cell carcinoma)	1
Gastroesophageal junction (adenocarcinoma)	1
Mesothelioma	1
Sex	
Male	8 (47%)
Female	9 (53%)
Race	
Caucasian	14
African American	3
Number of prior therapies, median (range)	3 (0–5)

Table 2

Dose escalation scheme and dose limiting toxicities

Dose level	# treated patients	# DLT
Continuous Level 1	4	2
V 280 mg/m2		- unstable angina
E 75 mg/day		- asthenia, mouth pain
Continuous Level −1	6	2
V 250 mg/m2		- nausea, vomiting
E 75 mg/day		- neutropenia, fatigue
Intermittent Level 1	7	2
V 280 mg/m2		- dehydration, mouth pain, abdominal pain, fatigue
E 75 mg/day		- dehydration, mouth pain, myalgias

Table 3

Most frequent adverse events

Adverse event	Patients affected, all grades # (%) (*n*=17)	# Patients with grade 3 or 4 as highest toxicity	# Cycles Affected, all grades (*n*=76 cycles)	# Cycles affected, grades 3 and 4
Leukopenia	13 (76%)	8	19	9
Neutropenia/ granulocytopenia	11 (65%)	8	14	8
Nausea	8 (47%)	3	10	3
Vomiting	8 (47%)	2	8	2
Fatigue (asthenia, lethargy, malaise)	7 (41%)	5	10	5
Anemia	6 (35%)	1	8	1
Pain (Bone, head, abdomen)	6 (35%)	3	9	3
Anorexia	5 (29%)	0	5	0
Diarrhea	5 (29%)	0	6	0
Pain—Other	5 (29%)	0	5	0
Hypokalemia	5 (29%)	3	9	5
Transaminitis	4 (24%)	0	6	0
Constipation	4 (24%)	0	4	0
Pain—Oral cavity	4 (24%)	0	4	0
Rash/desquamation	4 (24%)	0	5	0
Hyponatremia	4 (24%)	2	6	2
Hyperbilirubinemia	3 (18%)	0	3	0
Dehydration	3 (18%)	1	3	1
Dermatology/Skin—Other	3 (18%)	0	3	0
Hypernatremia	2 (12%)	1	2	1
Myalgias/ muscle weakness	2 (12%)	2	2	2
Dysphagia	1 (6%)	1	1	1
Pain—Cardiac/heart	1 (6%)	1	1	1
Hypophosphatemia	1 (6%)	1	1	1