A Phase II study of 9-nitro-camptothecin in patients with previously treated metastatic breast cancer

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Summary

Aims: This Phase II study was conducted to determine the efficacy and toxicity of 9-nitro-camptothecin (9-NC) in patients with previously treated metastatic breast cancer. Pharmacokinetic samples were obtained to investigate the correlation of plasma 9-NC exposure with clinical response and toxicity. Patients and methods: Eligible patients had histologically confirmed metastatic breast cancer with measurable or evaluable disease. Patients must have received one or two prior chemotherapy regimens for metastatic disease. 9-NC was given orally, 1.5 mg/m²/day for 5 days each week; response was assessed every 8 weeks. Pharmacokinetic samples were obtained on day 1 of weeks 1 and 5. Results: Eighteen patients were enrolled between September 1999 and May 2000; seventeen patients were evaluable for response. The most common toxicities were nausea, vomiting, urinary symptoms, fatigue and diarrhea. No objective responses were observed; six patients had stable disease. 9-NC apparent clearance ranged from 0.57 to 55.08 L/h (median 5.91 L/h); 9-NC area under the curve ranged from 38 to 2130 ng/ml × h (median 377 ng/ml × h). There was no relationship between pharmacokinetic parameters and individual patient toxicity. Conclusion: 9-NC has limited activity in patients with previously treated metastatic breast cancer. Though 9-NC has substantial pharmacokinetic variability in this patient population; no correlation was found between pharmacokinetic variables and toxicity.

Introduction

Breast cancer affects 180,000 women in the United States annually. Though early detection and advances in adjuvant therapy have decreased mortality, over 40,000 women succumb to metastatic breast cancer every year [1]. Many active agents are available for the treatment of metastatic breast cancer. Response rates of ≥30% are routinely achieved in previously untreated patients with several available chemotherapeutic agents. Response rates decrease significantly in patients with prior exposure to chemotherapy, particularly those with prior anthracycline treatment [2].

A recent Phase II trial of capecitabine reported a 20% response rate as third-line therapy in patients refractory to anthracyclines and taxanes, leading to Food and Drug Administration (FDA) approval [3]. Oral therapy offers several advantages for patients undergoing palliative treatment, including lack of need for a vascular access device and less time spent in clinic. The development of other effective oral chemotherapeutic agents would represent a significant advance in the care of women with metastatic breast cancer.

Camptothecins, derived from the tree Campotheca acuminata, are a unique class of chemotherapy agents that limit DNA synthesis by inhibiting topoisomerase I activity. Topoisomerase I expression is highly variable in human tumor samples [4] but in cell culture systems the expression and activity of
topoisomerase I predicts sensitivity to camptothecins. As the cytotoxicity of topoisomerase I inhibitors is S-phase specific, in vitro and in vivo studies have suggested that efficacy may be more dependent on prolonged exposure rather than brief exposure to high drug concentrations [5].

The initial development of camptothecins was limited by poor solubility and unpredictable toxicity, including myelosuppression, hemorrhagic cystitis, nausea, diarrhea, alopecia and dermatitis. Therefore, camptothecin analogues, including irinotecan (CPT-11), topotecan and 9-aminocamptothecin (9-AC), were developed [6,7]. Initial xenograft studies of 9-NC (Rubitecan, Supergen, San Ramon) using three different breast cancer cell lines found complete tumor regression after 28 days of treatment. Treatment was continued for 50 days after maximum response with no tumor regrowth observed. In addition the combination of 9-NC and trastuzumab (Herceptin, Genentech, South San Francisco) produced significant tumor regressions in HER2 overexpressing xenografts. No major toxicities were observed in these xenograft studies [8–10].

9-NC is orally absorbed with peak plasma levels occurring about 4 h (range 2–6 h) after ingestion; peak plasma concentrations of the lactone form appear 1 h after ingestion (range 0.5–6 h) [11]. About 5% of 9-NC appears unchanged in the urine, all in the lactone form. Drug decay measurements estimating area under the curve (AUC) determined approximately 13% of the total 9-NC measured was in the lactone form. No evidence of drug accumulation was found with chronic therapy [12].

In a Phase I study of 9-NC in patients with refractory malignancies, responses were observed in 6 of 29 patients, including one in a patient with advanced breast cancer. Dose-limiting myelosuppression was found only at doses ≥1.5 mg/m²/day; the maximum tolerated dose was 2 mg/m²/day. Grade 4 hematologic toxicities included anemia (11%), neutropenia (6%) and thrombocytopenia (9%). Other toxic effects seen at all dose levels were nausea (23%), vomiting (14%), diarrhea (20%) and chemical cystitis (23%).

This trial was designed to assess the efficacy and toxicity of 9-NC in patients with previously treated metastatic breast cancer. In addition, limited pharmacokinetics were performed to investigate the correlation of plasma 9-NC concentrations with clinical response and toxicity.

Patients and methods

Patients with histologically confirmed unresectable locally recurrent or metastatic adenocarcinoma of the breast with measurable or evaluable disease were eligible. Patients must have progressed after one or two prior chemotherapy regimens for metastatic disease; prior treatment with camptothecin analogs was not allowed. Patients were required to have a performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) scale, as well as adequate renal, hematologic and hepatic function. Effective contraception was required in all patients with child bearing potential. Patients with active central nervous system (CNS) metastases were excluded; patients with treated CNS metastases were eligible if they had completed radiation therapy at least 4 weeks prior to enrollment and did not require chronic corticosteroid treatment.

9-NC, 1.5 mg/m²/day based on actual body weight, was given orally each morning with juice or cola for five consecutive days followed by 2 days rest; daily doses were rounded to the nearest 0.25 mg. This weekly cycle continued until disease progression or unacceptable toxicity intervened. Patients were instructed to increase their total oral fluid intake to at least 3 L per day during treatment to reduce the risk of cystitis.

Dose modifications were specified for hematologic toxicity. A complete blood count was obtained at the beginning of each weekly treatment cycle. 9-NC was held for 1 week, then decreased to 1.5 mg/m²/day for 4 days each week if the absolute neutrophil count (ANC) was 500–999 cells/mm³ or the platelet count 50,000–99,999/mm³. If the ANC fell to ≤500 cells/mm³ or platelets ≤50,000/mm³ 9-NC was held for 1 week, then decreased to 1.0 mg/m²/day for 4 days each week. Grade 3 nonhematologic toxicities (except alopecia or nausea/vomiting) required 9-NC to be dose-reduced or held at the investigator’s discretion; treatment was held and dose reduced for all grade 4 nonhematologic toxicities.

Response was assessed every 8 weeks according to WHO criteria. Patients responding or stable continued therapy until progression or unacceptable toxicity. The study was designed to test the null hypothesis (H₀) that the true response rate is 10% versus the alternative hypothesis (Hₐ) that the true response rate is 25% with a power of 0.80 and a significance level of 0.05. Based on this design, up to 43 qualified patients could be enrolled in a two-stage