A novel combination of cisplatin, irinotecan, and capecitabine in patients with advanced cancer

Michael Jefford¹, Michael Michael¹, Mark A. Rosenthal¹, Ian D. Davis¹, Michael Green¹, Bev McClure¹, Jennifer Smith¹, Brigid Waite² and John Zalberg¹
¹Centre for Developmental Cancer Therapeutics, Melbourne, Victoria, Australia; ²Roche Products Pty Limited, Dee Why, NSW, Australia

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Summary
Background: We conducted a dose escalation study combining cisplatin, irinotecan, and capecitabine (CIC), aiming to establish the maximum tolerated doses (MTD), side effect profile, and dose-limiting toxicity (DLT) of this novel regimen. Patients and methods: Intravenous cisplatin and irinotecan were to be administered on days 1 and 8, and oral capecitabine on days 1–14 of a 3-week cycle. The study was conducted in three parts. Part A: escalating doses of irinotecan (40 → 80 mg/m²) and capecitabine (1000 → 3300 mg/d) combined with a fixed dose of cisplatin (30 mg/m²). Part B: escalating doses of irinotecan (MTD-A → MTD-A + 40 mg/m²) with fixed doses of cisplatin (20 mg/m²) and capecitabine (MTD-A level). Part C: escalating doses of capecitabine (1300 mg/d → 2600 mg/d) with fixed doses of cisplatin (20 mg/m²) and irinotecan (60 mg/m²). Results: Of 51 eligible patients 27 (53%) were male, median age was 58 years and 88% had PS 0–1. Major primary disease sites were colorectal (24%), unknown (14%), stomach (14%), and pancreas (12%). MTD-A was cisplatin 30 mg/m², irinotecan 60 mg/m², capecitabine 1000 mg/d and MTD-B was cisplatin 20 mg/m², irinotecan 90 mg/m², capecitabine 1000 mg/d. An MTD was not formally established for part C. DLTs consisted of infection with neutropenia (1), diarrhea and fatigue (1), hypokalemia (1), diarrhea and febrile neutropenia (1) and C2 delay of ≥2 weeks or 25% dose reduction in C1 due to neutropenia or thrombocytopenia (6). Seven patients had a partial response to treatment (four colorectal, one SCLC, one NSCLC, one unknown primary), twenty seven SD (53%), twelve PD (24%) and five NE (10%). Conclusion: CIC was associated with moderate toxicity and only modest antitumor activity. We conclude that this regimen has insufficient activity to justify further study in the phase II setting.

Introduction
Multi-agent, cisplatin-based chemotherapy regimens have a long-standing role in the treatment of advanced cancer. Doublets of cisplatin, irinotecan, and 5-fluorouracil (5-FU) have been studied in a variety of cancer types. The combination of cisplatin and infusional 5-FU represents standard therapy for several cancers including squamous cell carcinoma of the head and neck, nasopharynx, esophagus, and cervix [1–3]. Synergistic or additive activity has been observed between cisplatin and irinotecan in human tumor cell lines and xenograft models [4,5] and several phase II studies have suggested significant activity of this regimen [6–10]. Numerous studies have also suggested synergy between irinotecan and thymidylate synthetase inhibitors, including 5-FU. Irinotecan combined with 5-FU and leucovorin is considered a standard first-line treatment for metastatic colorectal cancer [11,12].

In patients with advanced colorectal cancer, 5-FU administered by protracted infusion results in higher response rates compared to bolus FU [13]. However, the use of infusional chemotherapy may be associated with medical complications, inconvenience, high costs, and poor quality of life. Central venous catheters
carry the risk of thrombosis and may be a focus for infection. Additionally, many patients would prefer to receive oral rather than intravenous treatment [14] and would prefer to have treatment at home rather than in the hospital [15].

The availability of oral fluoropyrimidines represents a significant development in this regard. Capecitabine is a rationally designed fluoropyrimidine carbamate, which is bioactivated by a three-enzyme process to provide prolonged high levels of the active moiety, 5-FU, in tumor cells [16]. Oral capecitabine is considered to be of similar efficacy to the use of bolus 5-FU [17,18], with a toxicity profile similar to infusional 5-FU. Capecitabine, compared to 5-FU, allows patients to avoid intravenous therapy and to receive treatment predominantly at home, rather than in hospital [19].

We designed a dose escalation study combining cisplatin, irinotecan, and capecitabine (CIC), based upon the proven synergy between 5-FU and both cisplatin and irinotecan, and also between cisplatin and irinotecan. This combination, or the combination of cisplatin, irinotecan, and 5-FU, has not been previously reported. We considered this to be a rational approach. The combination avoids the need for infusional therapy with its attendant potential complications and inconveniences. Additionally, as each of these agents may be administered within a 3-week cycle, the study design allowed for mainly outpatient-based treatment. Chief objectives of the study were: (1) to evaluate the toxicities of the CIC combination when given to patients with advanced cancer, and (2) to determine the maximum tolerated dose of capecitabine and irinotecan when combined with a fixed dose of cisplatin. We also aimed to record objective responses to the CIC combination in patients with advanced cancer.

Patients and methods

Patient selection

Patients with a histological or cytological diagnosis of advanced cancer were eligible. Patients were required to have measurable or evaluable disease. Other eligibility criteria included: age between 18 and 75 years; World Health Organization (WHO) performance status 0–2; predicted life expectancy ≥12 weeks; no exposure to topoisomerase I inhibitors within the preceding 3 months; no more than one prior chemotherapy regimen for advanced disease or in the neoadjuvant or adjuvant setting; and adequate hematopoietic (hemoglobin >90 g/L, neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L), hepatic (serum bilirubin ≤1.0 × the upper limit of normal (ULN), AST and/or ALT ≤3.0 × ULN), unless the liver was involved with tumor in which case AST and/or ALT ≤5.0 × ULN), and renal function (creatinine clearance ≥50 ml/min calculated using the Cockcroft–Gault formula). Patients with stable cerebral metastases were allowed. Specific exclusion criteria included: previous cumulative cisplatin dose ≥200 mg/m²; radiotherapy within the preceding 4 weeks or to ≥30% of bone marrow; lack of physical integrity of the upper gastrointestinal tract, or known malabsorption syndrome that may affect absorption of oral capecitabine, and hearing impairment or neuropathy of greater than grade 1 according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 2.

The trial was conducted at the clinical sites of the Centre for Developmental Cancer Therapeutics, Melbourne, Australia: Austin & Repatriation Medical Centre, Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Western Hospital. All patients gave written informed consent and the study was approved by the institutional review board/ethics committee at each site.

Treatment and dose escalation

Treatment was administered over a 3-week cycle, with capecitabine administered twice daily on days 1–14 and cisplatin and irinotecan administered intravenously on days 1 and 8. This treatment schedule was based upon previous studies using these agents within a 3-week treatment cycle. Patients were hydrated with normal saline (at least 500 mL) prior to receiving cisplatin. Cisplatin (in 500 mL normal saline) was administered as a 30–60 min intravenous infusion followed immediately by irinotecan (also in 500 mL normal saline) as a 30–60 min intravenous infusion. No other intravenous fluids were administered. Capecitabine was given orally divided into two doses 12 h apart on each day.

Dose escalation proceeded in three steps as indicated in Table 1. In step A, escalating doses of capecitabine and irinotecan were combined with a fixed dose of cisplatin (30 mg/m²). In step B: once the maximum tolerated dose (MTD) was reached in Step A, the cisplatin dose was reset to 20 mg/m²,