Phase I study of docetaxel and topotecan in patients with solid tumors

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Abstract Purpose: Both docetaxel (DOC), a promoter and stabilizer of microtubule assembly, and topotecan (TOPO), a topoisomerase I inhibitor, have shown antitumor activity in a variety of solid tumor malignancies. This phase I trial was conducted to determine the overall and dose-limiting toxicities (DLT) and the pharmacokinetics of the combination of DOC and TOPO in patients with advanced solid tumor malignancies. Methods: DOC was administered first at 60 mg/m² without G-CSF and at 60, 70, and 80 mg/m² with G-CSF by 1-h infusion on day 1 of the odd-numbered cycles (1, 3, 5, etc.) and on day 4 of the even-numbered cycles (2, 4, 6, etc.). TOPO 0.75 mg/m² was administered as a 30-min infusion on days 1, 2, 3 and 4 of each cycle. G-CSF 300 µg was administered subcutaneously (s.c.) on days 5–14. Cycles were repeated every 21 days. All patients were premedicated with dexamethasone 8 mg orally every 12 h for a total of six doses starting on the day before DOC infusion. Results: A total of 22 patients were treated. Six patients were treated in cohort I with DOC and TOPO doses of 60 and 0.75 mg/m², respectively, without G-CSF, and two patients developed DLT (febrile neutropenia). Four patients were treated in cohort II with DOC and TOPO doses of 60 and 0.75 mg/m², respectively, with G-CSF, and no DLT was observed. Four patients were treated in cohort III with DOC and TOPO doses of 80 and 0.75 mg/m², respectively, with G-CSF, and three developed DLT (febrile neutropenia). DOC was then de-escalated to 70 mg/m² and delivered with TOPO 0.75 mg/m² and G-CSF (cohort IV). Eight patients were treated at this dose level, and one DLT (febrile neutropenia) was observed. Two patients developed a severe hypersensitivity reaction shortly after the DOC infusion was started, one in cycle 1 and one in cycle 2. Both patients were removed from the study. Two patients developed severe dyspnea in the presence of progressive pulmonary metastases. Other nonhematological toxicities were mild. One patient with extensively pretreated ovarian carcinoma had a partial response, and eight patients with various solid tumor malignancies had stable disease with a median time to progression of 12 weeks (range 9–18 weeks). Administration of TOPO on days 1–4 and DOC on day 4 resulted in increased neutropenia. Conclusions: DOC 80 mg/m² given first as a 1-h infusion on day 1 with TOPO 0.75 mg/m² given as a 0.5-h infusion on days 1, 2, 3 and 4 with G-CSF was considered the MTD. The recommended phase II dose for DOC given on day 1 is 70 mg/m² with TOPO 0.75 mg/m² given on days 1, 2, 3 and 4 every 21 days with G-CSF 300 µg s.c. on days 5–14. The alternative schedule with DOC given on day 4 and TOPO on days 1–4 is not recommended.
**Key words** Docetaxel · Topotecan · Solid tumors · Phase I

### Introduction

Docetaxel is a semisynthetic agent of the taxane family. Like other members of its class, docetaxel promotes the assembly and stabilization of microtubules and thus prevents their depolymerization [1]. This leads to the formation of stable microtubule bundles that disrupt the equilibrium between polymerization and depolymerization and subsequently leads to cell death [2–4]. In contrast, the vinca alkaloids and colchicine inhibit tubulin polymerization, leading to disruption of the mitotic spindle [5]. Docetaxel inhibits the depolymerization of the microtubules approximately twice as effectively as paclitaxel. In addition docetaxel is capable of inducing phosphorylation and consequent inactivation of the antiapoptotic gene, bcl-2, with a 100-fold greater efficacy than paclitaxel [6–8]. Mechanisms of resistance to docetaxel are not completely understood.

Topotecan is a semisynthetic derivative of camptothecin, and is a topoisomerase I interactive agent [9, 10]. Topoisomerase I relieves torsional strain in DNA by inducing reversible, single-strand breaks [9, 11]. Topotecan binds to the topoisomerase I/DNA complex and prevents religation of the single-strand breaks [11]. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the complex formed by topotecan, topoisomerase I and DNA [11]. Mammalian cells cannot efficiently repair these double-strand breaks.

Docetaxel is extensively metabolized by cytochrome P450-3A4, and 98% of the drug is protein bound [12, 13]. The pharmacokinetics of docetaxel are not affected by age or sex, but the clearance of docetaxel is decreased with increasing z1-acid glycoprotein levels and impaired hepatic function [14, 15]. When docetaxel is administered in combination with cisplatin, its clearance is similar to that of single-agent docetaxel and is unaffected by the timing of cisplatin administration. The clearance of cisplatin is also unaffected, and cisplatin does not displace docetaxel from plasma proteins [16, 17].

Both docetaxel and topotecan are independently active in a wide variety of solid tumors [18–32] and have differing mechanisms of action [9, 14]. Some, though not all in vitro evidence suggests that taxanes and topotecan may have additive, or even synergistic, activity [33, 34]. Therefore, the combination of docetaxel and topotecan has potential for future development in many solid tumors. To date, there have been no studies to determine the sequence and toxicities of the combination of docetaxel and topotecan. We therefore conducted a phase I study of docetaxel and topotecan, alternating the sequence of administration of these agents. Docetaxel was administered on day 1 in odd-numbered cycles (1, 3, 5, etc.), and day 4 in even-numbered cycles (2, 4, 6, etc.), while topotecan was administered on days 1, 2, 3, and 4 of each cycle. The dose of docetaxel was escalated, and that of topotecan remained fixed. The dose of topotecan was not escalated due to our concerns of augmented myelosuppression.

### Patients and methods

#### Patient selection

Patients were required to have metastatic cancer for which no proven standard therapy was available. Radiographic documentation of metastatic disease was required. Patients also had to meet the following eligibility criteria: life expectancy ≥2 months, ECOG performance status ≤2, age ≥18 years, absolute neutrophil count (ANC) ≥1500/µl, platelet count (PLT) ≥100,000/µl, serum creatinine ≤1.5 mg/dl, 24-h urine creatinine clearance (CrCl) ≥50 ml/min, bilirubin ≤1.3 mg/dl, SGOT and/or SGPT not more than 2.5 times the institutional upper limit of normal (ULN) if alkaline phosphatase (AP) was less than ULN, or AP was up to four times ULN if SGOT and SGPT were ULN or less. Patients who had both SGOT and SGPT elevation more than 1.5 times ULN and AP more than 2.5 times ULN were not eligible for this study. At least 4 weeks must have elapsed from prior chemotherapy (6 weeks for nitrosoureas, and mitomycin C). Patients were not allowed to have undergone major surgery or radiation therapy within the 2 weeks preceding the start of treatment. If more than 25% of the pelvis had been irradiated, treatment was postponed for 4 weeks. All premenopausal women were required to have a negative pregnancy test and to use acceptable contraception. Patients with serious medical or psychiatric illnesses, which would prevent informed consent or intensive treatment, were excluded. All patients entering this study were informed of the investigational nature of the treatment and its potential side effects and were required to give written informed consent. This protocol was approved by the University of Maryland Institutional Review Board.

#### Treatment plan

Docetaxel, at the cohort-specific dose, was administered first by 1-h i.v. infusion on day 1 of odd-numbered cycles (1, 3, 5 etc) and day 4 of even-numbered cycles (2, 4, 6 etc). Topotecan was administered at a fixed dose of 0.75 mg/m² by 0.5-h i.v. infusion on days 1, 2, 3 and 4 of each cycle. Cycles were repeated every 21 days. The doses of docetaxel tested are shown in Table 1. In cohorts II, III and IV, G-CSF 300 µg subcutaneously (s.c) was given on days 5–14 of each cycle of chemotherapy. All patients received oral dexamethasone prophylaxis 8 mg twice daily for six doses, starting on the day before docetaxel treatment. This was done to prevent cumulative docetaxel-related edema. In addition all patients received emesis prophylaxis consisting of dexamethasone 10 mg orally daily and granisetron 2 mg orally immediately before chemotherapy. No other chemotherapy, radiation therapy or immunotherapy was permitted while patients were on study. Patients received full supportive care, including analgesics, transfusions of blood and blood products, antibiotics, and antiemetics, as indicated. A minimum of three patients were treated per cohort, and no intrapatient dose escalation was permitted. Responding patients remained on study until disease progression or the development of unacceptable toxicity. Patients who developed progressive disease at any time were removed from the protocol. Patients with stable disease could continue to receive therapy for up to six cycles beyond their maximum response. Patients were removed from the protocol if they developed an anaphylactic reaction to the chemotherapy agents, or if the termination was deemed in the best interest of the patient. Patients with hematologic dose-limiting toxicity (DLT) but also demonstrating a clinical or radiographic