Biweekly administration of 24-h infusion of irinotecan followed by a 1-h infusion of docetaxel: a phase I study

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We developed a chemotherapy combination regimen based on preclinical data suggesting synchronization of cancer cells in G_2/M phase when exposed to irinotecan over a protracted period. This phase I study aimed to determine the toxicity spectrum, and define the dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended optimal dose (ROD) of irinotecan infused over 24 h and followed by a 1-h infusion of 30 mg/m^2 docetaxel. Starting dose for irinotecan was 30 mg/m^2 and escalation proceeded at 30 mg/m^2 increments, in cohorts of three to six patients until the MTD was reached. A dose between the MTD and the previous level was explored to further define the ROD. Thirty-two patients with advanced refractory cancers (median age 64, 19 male) received 190 treatment courses at five dosing levels of irinotecan: 30 mg/m^2 ($n=6$ patients), 60 ($n=3$), 90 ($n=7$), 120 ($n=8$) and 105 ($n=8$). The MTD and ROD was 120/30 and 105/30 mg/m^2. DLTs were diarrhea and neutropenia. Antitumor activity was modest. The ROD of biweekly administration of 24-h irinotecan followed by 1-h docetaxel is 105 and 30 mg/m^2, respectively. The low hematological toxicity and modest activity observed leave questions concerning the optimal timing of this combination. ***Anti-Cancer Drugs*** **15:747–752 © 2004 Lippincott Williams & Wilkins.**

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Introduction

Irinotecan is a prodrug that is converted *in vivo* by carboxylesterase to active metabolite SN-38, a S-phase-specific DNA topoisomerase I inhibitor [1]. We considered preclinical data supporting the relevance of protracted infusion of camptothecin analogs. For irinotecan, pulsed infusions of high doses proved to be more active in cells expressing wild-type p53, whereas sustained exposure was found more efficient in cells expressing mutant p53 and also synchronized malignant cells in the G_2/M phase [2,3]. The potential for cancer cells to synchronize at an increased rate in the G_2/M phase on prolonged exposure to SN-38 make mitotic spindle poisons attractive candidates for such combinations while additive activity of irinotecan and taxanes when administrated sequentially further support clinical investigation of such a schedule [4]. Docetaxel is an antimitotic agent of proven clinical activity that makes it an ideal choice in such a combination [5,6].

We sought to define the optimal dose as well as the toxicity spectrum of prolonged infusion of irinotecan in combination with docetaxel in a phase I trial in cancer patients. We thought that a schedule of 24-h infusion of irinotecan followed by a 1-h infusion of docetaxel addressed both scientific rationale and clinical convenience. The every-2-week recycling of the treatment was selected because hematological toxicity of both engaged agents is known to resolve shortly [7,8].

This phase I trial was conducted between July 2000 and April 2002 at the Departments of Medical Oncology of the Ioannina University Hospital, Ioannina, Greece and AHEPA University Hospital, Thessaloniki, Greece, following approval by the local institutional review boards.

Patients and methods

Endpoints

The objectives of the study were to determine the maximal tolerated dose (MTD), recommended optimal dose (ROD) and dose-limiting toxicities (DLT), and assess the spectrum of toxicities of the combination of irinotecan infused i. v. over 24 h followed by a 1-h infusion of docetaxel and administered every 2 weeks. Although not a formal endpoint for a phase I study, recording of the antitumor activity of the combination was deemed appropriate in evaluable cases.

Eligibility criteria

Eligibility criteria for all patients included age higher than 17 years, performance status 0–2 on the WHO scale, life expectancy of at least 12 weeks, adequate bone marrow [white blood cell count (WBC) $> 3.5 \times 10^9$/l, absolute neutrophil count (ANC) $> 1.5 \times 10^9$/l, platelet count

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$> 100 \times 10^9$/l], renal [serum creatinine $< 1.5 \times$ upper limit of normal (ULN)] and hepatic (serum bilirubin $< 1.25 \times$ ULN, serum transaminases $< 2 \times$ ULN or $< 5 \times$ ULN in the presence of liver metastases) function, and absence of clinically relevant neuropathy, psychiatric illness, pregnancy or lactation. Patients were to have histologically or cytologically proven locally advanced or metastatic solid tumors. Any previous chemotherapy should have been discontinued at least 4 weeks (6 weeks for nitrosoureas, melphalan and mitomycin C) before enrollment. Extended field radiotherapy should have been stopped at least 6 weeks prior to study entry, whereas concurrent limited field radiotherapy was allowed. Before enrollment in the trial, all patients provided written informed consent.

Dose-escalation schema

Decisions on dose escalation were made by the two primary investigators (E. B. and G. F.) upon considering accumulating data in an electronic database at the Ioannina University Hospital that was updated on a weekly basis.

The docetaxel dose was maintained unchanged at 30 mg/m^2 and was administered i.v. over 1 h following completion of a 24-h infusion of irinotecan. This dose was selected as a low-toxic dose of docetaxel shown active in weekly and biweekly schedules of administration according to our own and other's experience [9,10].

The starting dose for irinotecan in the first cohort was 30 mg/m^2. Escalation was planned at 30 mg/m^2 increments in consecutive cohorts of three to six patients depending on the occurrence of toxicity. In the absence of major toxicity three patients would be enrolled per dose level. In the case of occurrence of a DLT in the first three patients of any cohort, a total of six patients were to be treated at that dose level. Dose escalation could continue if no further DLTs were observed in all six patients (1/6). Whenever two DLTs occurred within a maximum of six patients, the assumption would be made that the MTD had been reached. Upon definition of the MTD, an intermediate dose between the MTD and the immediately lower dose level would be studied and, if found well-tolerated, characterized ROD.

Treatment administration

Treatment was scheduled to be given every 2 weeks. Irinotecan was administered on day 1 as a 24-h i.v. infusion in 15 ml of 5% dextrose in water (D5W) solution infused by ambulatory electronic microinfusion pump (Micrel MP20; France) set at a flow rate of 20 ml/24 h and connected to a central venous access device. Docetaxel was infused i.v. in 250 ml 0.9% normal saline (NS) solution over 60 min at the end of irinotecan infusion on day 2. Prophylactic ondansetron 8 mg and dexamethasone 8 mg were injected i.v. 30 min prior to both irinotecan (day 1) and docetaxel (day 2) administration. Additional antiallergic medication was injected i.v. prior to docetaxel infusion in the form of dimetindene maleate 4 mg and ranitidine 50 mg. Subcutaneous administration of granulocyte colony stimulating growth factor (G-CSF; filgrastim) at a dose of 5 mg/kg body weight was allowed to utilized only upon occurrence of febrile neutropenia or a National Cancer Institute Common Toxicity Criteria (NCI CTC, version 2.0) grade 4 neutropenia lasting more than 5 days at any cycle of treatment.

Patients who experienced an objective response or clinical benefit continued therapy to a maximum of eight cycles (16 courses), toxicity permitting. Patients with progressive disease or unacceptable toxicity discontinued treatment and were taken out of the study.

Evaluation of toxicity

Chemotherapy toxicity was graded according to the NCI CTC [11]. Full blood count was assessed weekly, while performance status, full biochemical profile and clinical assessment were assessed every 2 weeks, prior to chemotherapy administration. Dose escalation and determination of DLTs and MTD were performed on the basis of toxicity recorded up to the first two cycles (four courses) of treatment in each patient. Patients receiving at least two treatment courses were considered evaluable for toxicity.

DLT was defined any toxicity causing a more than a 2-week delay in the administration of the next treatment course, any grade 4 hematological toxicity, any grade 3 or 4 non-hematological toxicity except alopecia, nausea, vomiting and the combination of diarrhea of grade 2 or higher with grade 3 or higher neutropenia. MTD was defined as the dose-level at which DLTs occurred in at least one-third of a six-patient cohort. Patients who did not complete two courses of chemotherapy because of reasons not related to toxicity (withdrawal of consent, rapid disease progression, rapid decline of performance status) were replaced in the determination of DLT and MTD, but were included in overall toxicity analyses.

Dose modification and delays

Chemotherapy was only given when appropriate hematological reserves were present (WBC $> 3.0 \times 10^9$/l with ANC $> 1.5 \times 10^9$/l, platelet count $> 100 \times 10^9$/l) and after recovery from significant non-hematological toxicity (grade 0–1). If this was not the case, treatment was delayed until after hematological recovery, resolution of other organ toxicity or for a maximum of 2 weeks. In the case of occurrence of DLT or other clinically significant toxic effects, when further treatment was deemed to be beneficial for the patient, therapy was continued off study at the immediately lower dose level, based on the

clinical judgment of the investigator. Dose modifications were not allowed in this study.

Evaluation of response

Patients completing at least four courses of treatment with at least one tumor assessment were considered evaluable for response. Tumor assessment for all patients was performed at baseline, within 4 weeks from initiation of treatment and thereafter every four treatment courses and every 2 months on follow-up until tumor progression was documented. Chest X-rays and computerized tomographic (CT) scans were used for objective tumor assessment. Response was evaluated by using the RECIST criteria for solid tumors [12]. When an objective response was observed, all assessments were to be repeated in 28 days to confirm the response. The duration of objective responses were calculated from the time the response was first documented until the date of disease progression. The duration of stable disease dated from the commencement of treatment to the date of disease progression.

Ethical considerations

Independent Ethical Committees at the two centers involved approved the study protocol and the patient informed consent form. Informed written consent was obtained from each patient prior to enrolment. The trial was carried out in accordance to the principles of the Declaration of Helsinki and the European Note for Guidance for Good Clinical Practice.

Monitoring

The study was monitored by the data office of the Medical Oncology Department of the Ioannina University Hospital on the basis of a regular weekly updating of an electronic database. Clinical data made available during the course of the study was considered in making a judgment for proceeding with the trial. Clinical investigators entered the information required by the protocol onto Clinical Report Forms and forwarded them to the data office unit of the Medical Oncology Department of the Ioannina University Hospital. Data quality assurance was carried out by complete checking of data by two monitors.

Results

From July 2000 until April 2002, 32 enrolled patients received a total of 190 treatment courses (median number of treatments administered per patient = 4, range 1–16). Four registered patients were dropped from the study because they failed to start treatment due to logistic reasons. The median patient age was 63 years (34–75) and both sexes were represented (males 19 and females 13). Most patients were symptomatic, but with a good performance status and managed to receive an adequate number of treatment courses. All treated patients had advanced malignancies, more commonly gastric adenocarcinoma and head and neck squamous carcinoma. Among the patients, 21 had received previous chemotherapy, 14 of them two or more regimens. Eleven patients were chemonaive, among whom the diagnosed malignancies were gastric cancer ($n = 6$), pancreatic cancer ($n = 2$), cancer of unknown primary ($n = 2$) and cholangiocarcinoma ($n = 1$). The patient characteristics at baseline and dose-escalation data are seen in Tables 1 and 2, and recorded toxicity in Table 3.

MTD, DLTs and ROD

The MTD of biweekly administration of 24-h irinotecan followed by 1-h docetaxel was 120 and 30 mg/m^2, respectively. The DLTs observed in each dose level are concisely shown in Table 4. One episode of grade 3 diarrhea occurred during the second course of treatment in a patient treated in cohort 90/30, but resolved within 48 h with oral hydration and loperamide therapy. In the MTD cohort, the DLT consisted of three episodes of grade 3 diarrhea, one episode of uncomplicated grade 4 neutropenia of 7 days duration and one episode of febrile neutropenia. The patients who experienced grade 3 diarrhea were managed with oral therapy and had their symptoms resolved within 48 h. Febrile neutropenia occurred during the fourth treatment course of a patient with head and neck cancer. He was treated with i.v. fluids and broad-spectrum antibiotics; his fever resolved in 48 h and neutropenia in 4 days. The 105/30 cohort was defined

Table 1 Patient characteristics

Patients	32
Gender (M/F)	19/13
Age (years) [range (median)	34–75 (63)
PS [range (median)]	0–2 (1)
Prior chemotherapy	
naive	11
pretreated	21
Diagnosis	
gastric	10
H/N	5
CUP	4
lung	3
pancreatic	3
hepatocellular	1
ovarian	3
breast	1
bile duct	1
colon	1

Table 2 Treatment characteristics

Dose (mg/m^2)	No. of patients	Treatment courses		Totals
		Range	Median	
30/30	6	1–16	11	51
60/30	3	3–6	3	12
90/30	7	2–12	4	42
120/30	8	1–12	5	37
105/30	8	2–12	5	48
Total	32			190

Table 3 Toxicity

	Dose level														
	30/30			60/30			90/30			120/30			105/30		
Patients treated	6			3			7			8			8		
Toxicity grade	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4
Febrile neutropenia			–			–			–			1			–
Infection	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hematological															
anemia															
leukopenia	–	–	–	–	–	–	1	1	–	5	–	–	–	–	–
neutropenia	–	1	–	–	–	–	3	1	–	2	3	1	1	–	–
thrombopenia	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Gastrointestinal															
diarrhea	–	–	–	–	–	–	1	1	–	5	3	–	4	2	–
constipation	1	–	–	–	–	–	–	–	–	–	–	–	1	–	–
nausea	2	–	–	1	–	–	1	–	–	2	–	–	4	–	–
vomit	2	–	–	–	–	–	4	–	–	–	1	–	1	–	–
hiccup	1	–	–	–	–	–	1	–	–	–	–	–	–	–	–
mucositis	–	–	–	–	–	–	–	–	–	1	–	–	1	–	–
anorexia	1	–	–	1	–	–	2	–	–	3	–	–	1	–	–
Constitutional															
fatigue	3	–	–	–	–	–	1	–	–	1	–	–	2	–	–
fever	–	–	–	1	–	–	1	–	–	3	–	–	–	–	–
Cardiovascular															
edema	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dermatological															
alopecia	5			3			3			2			3		
pruritis	–	–	–	–	–	–	1	–	–	1	–	–	–	–	–
Neurological															
insomnia	–	–	–	–	–	–	–	–	–	3	–	–	1	–	–
dizziness	–	–	–	2	–	–	–	–	–	–	–	–	–	–	–
Pain															
arthralgia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
myalgia	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–
headache	–	–	–	2	–	–	–	–	–	–	–	–	–	–	–

Table 4 DLT

	Dose level (irinotecan/docetaxel)				
	30/30	60/30	90/30	120/30	105/30
No. patients	6	3	7	8	8
Non-hematological grade ≥ 3	–	–	1	3	2
Hematological any grade 4	–	–	–	2	–
Diarrhea grade ≥ 2 plus ANC grade ≥ 3	–	–	–	–	–
Treatment delay >2 weeks	–	1	–	–	–

as the ROD for this scheme. At this dose level two patients experienced grade 3 diarrhea, one of them with fever. Both toxic episodes resolved with oral hydration, loperamide and ciprofloxacin (in the case of the febrile patient) within 48 h.

Hematological toxicity

Hematological toxicity was mild throughout the study up to the MTD. Grade 3 or 4 myelosuppression occurred rarely and without clinical sequela. In the first three cohorts (irinotecan/docetaxel 30/30, 30/60 and 30/90 mg/m^2) only two episodes of transient grade 3 neutropenia were observed in two patients. At the MTD level (irinotecan/docetaxel 120/30 mg/m^2) five episodes of grade 3/4 neutropenia were observed in four patients. Two of these episodes (uncomplicated grade 4 neutropenia and febrile neutropenia) constituted DLTs. The median duration of all grade 3/4 neutropenic episodes was 3 days. Among the eight patients who were enrolled in the expanded I-D 105/30 cohort, none experienced severe myelosuppression. Detailed information on hematologic toxic effects of treatment, including anemia, is reported in Table 3.

Non-hematological toxicity

The most common non-hematologic side-effects observed in this patient population were diarrhea, nausea/vomiting, anorexia, alopecia and fatigue. The vast majority of these events were mild and easy to manage. Detailed data on the non-hematological toxicity profile in each cohort are shown in Table 3. Three patients treated at the I-D 120/30 cohort experienced severe diarrhea

necessitating light diet, oral hydration and high-dose loperamide treatment (2 mg every 2–4 h). All patients experienced resolution of symptoms and signs within 48 h. Two episodes of grade 3 diarrhea (one of them with fever) in two patients treated at the 105/90 cohort resolved uneventfully with oral treatment and ciprofloxacin. One patient treated at the MTD cohort suffered a 24-h episode of intractable vomiting, controlled with metoclopramide suppositories and ondansetron 8 mg i.v. for two doses. Generally non-hematologic toxicity was mild. No toxic fatalities occurred in any of the 32 enrolled patients.

Treatment discontinuation

Reasons for discontinuation were progressive disease ($n = 18$), completion of treatment ($n = 2$), patient's wish ($n = 3$), death unrelated to malignant disease or its treatment ($n = 1$) and occurrence of DLT ($n = 8$). Among the patients who went off-study due to DLT, four patients opted to continue treatment at a lower dose and two patients with G-CSF support.

Tumor response data

Twenty-two patients were evaluable for tumor response to the study regimen. Only one partial remission was documented. This objective response occurred in a chemonaive 65-year-old patient with metastatic non small cell lung cancer treated at the I-D 105/30 dose level. The tumor response lasted for 10 months. Five more patients with various malignancies (gastric cancer $n = 2$, non-small cell lung cancer $n = 2$, and head and neck cancer $n = 1$), treated at the three higher dose levels (90/30, 105/30 and 120/30) had disease stabilization for a median of 4 months.

Discussion

Exposing malignant cells over prolonged periods to S phase cytotoxics is supposed to result in increased fractional cell kill and superior antitumor efficacy. Such a hypothesis has been successfully tested in the case of 5-fluorouracil protracted infusion [13] and is undergoing clinical evaluation over the last few years for topoisomerase poisons [14–16].

Emerging data from phase II studies support a favorable modulation of the typical irinotecan toxicity profile with long infusion schedules. Myelosuppression is mild, in contrast to 3-weekly regimes of short infusion. The most common toxicity is diarrhea which seems to be manageable, while encouraging preliminary evidence of antitumor activity has emerged from the early phase I trials [16,17]. Investigators have reported high AUC ratios of SN-38 to irinotecan for prolonged administration, a finding that lends weight to the principle of more efficient conversion of the prodrug to the active metabolite [18].

In our study, 24-h irinotecan infusion followed by docetaxel was indeed associated with mild toxicity. Severe or clinically relevant myelosuppression was absent, allowing escalation of the combination to the 120/30 mg/m^2 every 2 weeks dose level. The most common dose-limiting toxicity was diarrhea, although easily manageable. Such gastrointestinal side-effects defined the recommended dose of the irinotecan/docetaxel combination as 105/30 mg/m^2. The lack of significant bone marrow ablation may well be due to lower systemic peak levels of SN-38 and the more efficient detoxification of SN-38 by means of glucuronidation by rate-dependent hepatic enzymes. The relatively low dose intensity of docetaxel administered may also have contributed towards the bone marrow-sparing effect [19,20].

Both irinotecan and docetaxel have been shown to be active against a variety of solid tumors, such as lung cancer, gastrointestinal malignancies and breast cancer to name a few [21–24]. In our study, the observed antitumor activity of this regimen was modest. Even among seven chemonaive patients that had not received chemotherapy before, six of whom had gastric adenocarcinoma, we failed to obtain an objective response. In a recently published phase II study single-agent irinotecan yielded as upfront therapy a 20% response rate in metastatic gastric cancer [24]. We must say that our patients were treated over a wide range of irinotecan dosages and response was not an endpoint for a phase I trial. However, our findings, when evaluated in the light of preclinical data and the demonstrated clinical activity of engaged compounds such as single agents and standard every-3-week administration by short infusion, raises questions about the optimal sequence and timing of administration of the combined agents [25,26].

In this study we opted to use the irinotecan followed by docetaxel sequence in view of evidence of G_2/M arrest of cells caused by irinotecan in human tumor cell lines. Synchronization of tumor cells in the G_2 or M phase of the cell cycle could result in increased fractional cell kill upon exposure to a G_2/M-specific cytotoxic drug such as docetaxel [2,3,27]. We consider as a most likely explanation of the unexpectedly low anti-tumor activity of this schedule a failure of irinotecan to achieve efficient synchronization of cancer cells. It seems that either the duration of infusion of irinotecan or the time interval allowed between the end of irinotecan infusion and administration of docetaxel was insufficient to expose cancer cells synchronized to the antimitotic action of docetaxel. Our speculation is also supported by *in vitro* data showing that the number of arrested cells in G_2/M phase upon exposure to topoisomerase I inhibitors is 3% lower than baseline immediately after the exposure, but 37% higher than baseline 28–32 h later [28].

We did not perform pharmacokinetics in this study that could possibly provide insight into potential interaction of two agents, but published studies have clearly shown that pharmacokinetics of both docetaxel and irinotecan are not modified with the administration schedule [26,29]. Furthermore, irinotecan and docetaxel have been combined in all sequences (irinotecan followed by docetaxel or vice versa) in phase I/II studies without any obvious differences in terms of activity or toxicity when the standard short infusion times were applied [25,26,30,31].

Overall, we showed that irinotecan can be safely administered on an outpatient basis every 2 weeks as a 24 h infusion followed by docetaxel at the recommended dose of 105/30 mg/m^2. However, the mild toxicity profile of the combination and the modest activity seen suggests the need of optimization of the administration schedule. This could regard both duration of infusion of irinotecan and timing and dose intensification of the taxane in further phase I/II trials.

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