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ORIGINAL ARTICLE

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Biweekly docetaxel-irinotecan with filgrastim support in pretreated breast and non-small-cell lung cancer patients. A phase I study

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Abstract *Background*: Docetaxel (DTX) has been shown to be a very active drug in both breast cancer (BC) and non-small-cell lung cancer (NSCLC). Irinotecan (CPT-11) is also active in NSCLC, and has shown promising antitumor activity in pretreated BC. *Purpose*: To define the MTDs of these two drugs given together every other week with the use of filgrastim support in pretreated BC and NSCLC patients. *Patients and methods*: Patients (aged 18–70 years, performance status ≤ 2) with advanced NSCLC or BC who had received at least one prior chemotherapy regimen were candidates for this phase I study. The starting DTX and CPT-11 doses were 60 mg/m^2 and 80 mg/m^2. Doses were alternately escalated at each step by 10 mg/m^2 for both drugs. Filgrastim 300 μg/day was given subcutaneously from days 4 through 7 of each cycle. *Results*: From April 2000, 41 patients were included in the trial (27 BC, 14 NSCLC). All BC patients had received epirubicin plus paclitaxel (with or without cisplatin) as first-line treatment. Of the 14 NSCLC patients, 12 had received cisplatin-based first-line therapy, and 8 patients had been pretreated with paclitaxel. The dose escalation proceeded through five dose levels up to DTX and CPT-11 doses of 80 mg/m^2 and 100 mg/m^2, respectively. Overall, ten patients showed dose-limiting toxicity during the first cycle, diarrhea in seven and neutropenia in the remaining three. Considering all 218 cycles delivered, grade 3 or 4 neutropenia occurred in 14 patients (34%), with only one episode of neutropenic fever, while severe diarrhea was observed in 9 patients (23%). A total of 21 objective responses were registered (four complete) for an overall response rate of 51% [95% CI 35–67]. A major response was seen in 16 of the 27 BC patients (59%) and in 5 of the 14 NSCLC patients (36%). *Conclusions*: DTX and CPT-11 can be safely given together biweekly at adequate doses, with filgrastim support. In view of the promising activity data in both groups, phase II studies testing this combination in pretreated BC and NSCLC patients are ongoing.

Keywords Docetaxel · Irinotecan · Breast cancer · Non-small-cell lung cancer

Introduction

Docetaxel (DTX) has been shown to be a very active drug in both breast cancer (BC) and non-small-cell lung cancer (NSCLC) [6, 20, 27, 32]. Single-agent irinotecan (CPT-11) has also shown definite antitumor activity in patients with advanced NSCLC either chemonaive or pretreated [8, 16, 17].

The role of CPT-11 in patients with advanced (BC) has been less-frequently addressed. However, there is some preclinical and clinical evidence supporting its efficacy in this disease. In an in vitro study, CPT-11, doxorubicin, topotecan, and cisplatin were tested against colon, lung and breast cancer cell lines. CPT-11 was shown to be the most effective drug [3]. In a phase II randomized trial testing two different CPT-11 schedules in refractory BC patients, a 29% overall response rate (ORR) was found [23]. In preclinical studies [22], the sequential administration of DTX and CPT-11 has shown at least supra-additive cytotoxicity in human lung cancer cell lines, and the order of administration does not seem to matter. In a preclinical three-arm dose-response study, combinations of DTX and CPT-11 at different doses and the maximal tolerated doses (MTD) of each agent were compared in nude mice transplanted with subcutaneous mammary adenocarcinoma 16/C. The optimal combination was found to be highly active

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with a 5.5-log cell kill (i.e. one log greater activity than the best cell kill with single-agent DTX). These dosages corresponded to 88% of the DTX and 54% of the CPT-11 highest non-toxic doses. In addition, excellent activity was retained at the three dose levels below the optimal one [2].

In a Japanese phase I study conducted in chemonaive NSCLC patients, the combination of DTX and CPT-11 was tested. CPT-11 was given on days 1, 8 and 15, and DTX on day 2, with a 4-week cycle. The recommended doses for phase II were DTX 50 mg/m^2 and CPT-11 50 mg/m^2 [18]. French investigators administered the two drugs together on day 1 every 3 weeks. The recommended doses of DTX and CPT-11 were 60 mg/m^2 and 275 mg/m^2. However, grade 4 neutropenia occurred in 85% of patients and 22.5% of patients experienced sepsis [5].

In view of these findings, we planned the present phase I study with the aim of determining the MTDs of DTX and CPT-11 given together every 2 weeks, with filgrastim support, in refractory BC and NSCLC patients.

Methods

Eligibility criteria

Patients with histologically or cytologically confirmed locally advanced (IIIB) or metastatic BC or NSCLC, with at least one prior chemotherapy for advanced disease, were considered eligible. Other eligibility requirements were: measurable tumor, age <70 years, ECOG performance status <2, adequate bone marrow function (ANC $\geq 2\times10^9$/l, platelet count $\geq 100\times10^9$/l, and hemoglobin level ≥ 100 g/l), liver function (bilirubin level less than 1.5 times the upper limit of normal, AST and/or ALT less than three times the upper limit of normal, prothrombin time less than 1.5 times control), renal function (creatinine clearance ≥ 60 ml/min), and cardiac function (absence of severe cardiac arrhythmia or heart failure, second- or third-degree heart block or acute myocardial infarction within 4 months prior to study entry). Previous or concurrent malignancy, were also considered as exclusion criteria, except for inactive nonmelanoma skin cancer, in situ carcinoma of the cervix, or other cancer if the patient had been disease-free for more than 5 years. CNS metastases were not considered an exclusion criterion if asymptomatic. A life expectancy of at least 12 weeks was also required. All patients gave their written informed consent, and the trial was approved by the Independent Ethical Committee of the National Tumor Institute of Naples.

Pretreatment evaluation

Pretreatment evaluation included a complete history and physical examination, ECG, chest radiograph, fiberoptic bronchoscopy, and chest and upper abdomen computed tomography for NSCLC patients. Radionuclide scan of bone, and CT scan of brain were also performed as necessary to document disease extent.

In BC patients mammography, chest radiography, liver ultrasonography, radionuclide scan of the bone (with radiographic evaluation of suspicious bone segments), and CT scan of the brain (in case of suspicion of brain involvement) were mandatory at the beginning of chemotherapy. Laboratory investigation included a complete blood cell count with WBC differential and platelet count, a full chemistry profile, prothrombin time, urinalysis, and determination of serum levels of tumor markers specific for either BC or NSCLC.

Treatment

Eligible patients received on day 1 every 2 weeks escalating doses of DTX (starting at 60 mg/m^2) and CPT-11 (starting at 80 mg/m^2). DTX was suspended in 250 ml 0.9% sodium chloride and infused over 60 min. It was followed by CPT-11 diluted in 250 ml sodium chloride and infused over 90 min. To prevent a hypersensitivity reaction to DTX, dexamethasone 8 mg was administered intravenously 30 min before starting the infusion, and 4 mg intramuscularly for 2 days after the infusion. Anti-5-hydroxytryptamine-3 receptors were systematically given to prevent emesis. Atropine was always given 30 min before CPT-11 infusion to prevent cholinergic syndrome. Filgrastim 300 μg/day was also administered on days 4 through 7. In case of delayed diarrhea, patients were given loperamide (one capsule every 2 h for at least 12 h, and for 12 h after the last liquid stool). If diarrhea persisted for more than 48 h patients were hospitalized and received intravenous forced hydration.

Chemotherapy was delivered at full doses if ANC was $\geq 2\times10^9$/l and platelets were $\geq 100\times10^9$/l. If WHO grade 1 neutropenia (1.5–1.9×10^9/l) or thrombocytopenia (75–99×10^9/l) was present on day 1, the treatment was delayed 1 week. If these values of neutrophils or platelets persisted after a 1-week delay, chemotherapy was administered at doses reduced to 75%. In the presence of grade 2 or more neutropenia or thrombocytopenia, treatment was always omitted. Doses of both drugs were reduced by 25% if grade 4 neutropenia or thrombocytopenia occurred, or if grade 3 or more non-hematologic toxicity had occurred in the previous course. Filgrastim was also allowed in the presence of grade 4 neutropenia lasting more than 3 days, or neutropenic fever, or if grade 2 or more neutropenia persisted for 2 weeks after the scheduled start of the next cycle. The treatment was definitively discontinued if grade 1 or more neutropenia or thrombocytopenia, or major non-hematologic toxicity persisted for three or more weeks after the scheduled start of the next cycle.

Dose-escalation criteria

Eligible patients received on day 1 escalating doses of DTX (starting at 60 mg/m^2) and CPT-11 (starting at 80 mg/m^2) every 2 weeks. Doses of each drug were alternately escalated at each step by 10 mg/m^2. The dose escalation was stopped if dose-limiting toxicity (DLT) occurred during cycle 1 in more than 33% of patients. Intrapatient dose escalation was not allowed. DLT was defined as the occurrence after the first cycle of WHO grade 4 neutropenia or thrombocytopenia lasting longer than 3 days, grade 4 anemia, grade 3 or more non-hematologic toxicity (except for nausea or alopecia), neutropenic fever or symptomatic thrombocytopenia. The lack of hematologic recovery by day 15 (any grade of neutropenia or thrombocytopenia) was also considered as a DLT.

We decided to consider grade 4 neutropenia lasting for 3 days or more as a DLT since we thought it would be unsafe to perform a further dose escalation in patients who had shown such a toxicity in spite of the 4-day prophylactic administration of filgrastim.

Toxicity and response evaluation criteria

Toxicities and response were graded according to the WHO criteria [19]. Hematologic toxicity was assessed performing blood cell counts and differential twice weekly and the worst toxicity was reported.

All patients underwent complete tumor response assessment after every four treatment cycles. Physical examination and routine laboratory tests were performed before each chemotherapy course, and all the diagnostic procedures required to evaluate response to treatment were performed after the fourth and eighth course. Complete response (CR) was defined as the complete disappearance of all tumor lesions, lasting at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the

products of the longest perpendicular diameters of all lesions. Stable disease (SD) was defined as a decrease of less than 50% in the sum of the products of the longest perpendicular diameters of all lesions. Progressive disease (PD) was defined as an increase of at least 25% in the sum of the products of the longest perpendicular diameters of all lesions, or as the appearance of any new lesion not previously identified.

A minimum of 4 weeks was required to document a response. Duration of response was measured from the date of registration to the date of documentation of progressive disease. Overall survival was measured from the date of registration to the date of death, and estimated by the Kaplan-Meier method [12]. All patients were included in the analysis of response and survival on an "intent to treat" basis. Therefore, the early discontinuation of treatment due to any cause was considered as a treatment failure, and included in the denominator of the response rate.

Follow-up assessment

Physical examination, routine laboratory tests, chest radiography, chest CT, and liver CT or ultrasonography were performed at 2-month intervals after discontinuation of treatment.

Results

Demographics

The characteristics of the 41 enrolled patients are outlined in Table 1. Of the 41, 27 had BC and 14 NSCLC. Their median age was 59 years (range 34–70 years). All 27 BC patients had received epirubicin plus paclitaxel with or without cisplatin as first-line treatment for their advanced disease. Only 2 had locally advanced disease, refractory to first-line chemotherapy. Among the remaining 22 patients, 14 had shown metastatic disease at diagnosis, and 8 had previously undergone surgery (7 with subsequent adjuvant chemotherapy), and at first relapse had received epirubicin plus paclitaxel, with or without cisplatin. Of these patients, 15 after first-line failure had received a regimen including gemcitabine plus cyclophosphamide and 5-fluorouracil/folinic acid [18].

Of the 24 NSCLC patients, 22 had received a cisplatin-based regimen (cisplatin plus gemcitabine, cisplatin plus vinorelbine, cisplatin plus gemcitabine and vinorelbine, or cisplatin plus gemcitabine and paclitaxel). The remaining 2 patients had received a non-platinum based regimen (Taxol plus gemcitabine and vinorelbine). Overall, 8 NSCLC patients had received paclitaxel in first-line.

Table 1 Demographics

Characteristic	Breast cancer	NSCLC	Total
Sex			
Male	0	11	11
Female	27	3	30
Age (years)			
Median	54	61	59
Range	34–70	42–69	34–70
Stage			
IIIB	2	3	5
IV	25	11	36
ECOG performance status			
0	4	0	4
1	16	8	24
2	7	6	13
Main metastatic sites			
Breast	2	0	2
Lung	4	3	7
Liver	7	4	11
Bone	10	3	13
Adrenal	0	1	1
Soft tissue	1	0	1
Brain	3	3	6
Response to front-line			
No	4	6	10
Yes			
< 3 months	6	3	9
3–6 months	11	4	15
> 6 months	6	1	7
Total	27	14	41

Dose-escalation results

Table 2 summarizes the dose-escalation data. Patients were accrued through five different dose levels, for a total of 218 cycles delivered. At the first dose level (DTX 60 mg/m^2, CPT-11 80 mg/m^2) four BC and two NSCLC patients were recruited. One BC patient showed severe diarrhea after the first cycle. She had massive liver involvement. After this DLT, doses were reduced by 25% in the subsequent cycles, and she was able to complete the treatment plan without further episodes of severe diarrhea. Five BC and two NSCLC patients were included at dose level 2 (DTX 60 mg/m^2 and CPT-11 90 mg/m^2). Two DLTs occurred during the first cycle, consisting of grade 3 diarrhea and grade 4 neutropenia longer than 3 days, respectively. The episode of severe diarrhea occurred in a 68-year-old BC patient with massive liver involvement. Liver enzyme (AST, ALT, alkaline phosphatase) serum levels were abnormal at the beginning of treatment, although total bilirubin did not exceed 1.5 mg/dl. Grade 4 neutropenia was observed in a 61-year-old NSCLC patient with multiple bone metastases who had received a triplet regimen as first-line therapy.

Five BC and three NSCLC patients were recruited at dose level 3 (DTX 70 mg/m^2 and CPT-11 90 mg/m^2). Two DLTs occurred during the first cycle in this cohort. One NSCLC patient showed grade 4 diarrhea which required hospitalization. He had received three cycles of a triplet regimen as first-line therapy, and six cycles of XR 5000, an inhibitor of both topoisomerases I and II, as salvage treatment. Treatment was resumed at 75% of the planned doses in the subsequent cycles, and no further episodes of severe hematologic or non-hematologic toxicity occurred. The other DLT was grade 3 neutropenia persisting on day 15 in a BC patient aged 67 years, with bone and lung localizations.

Table 2 Dose-escalation results

Dose level	DTX/CPT-11 (mg/m^2)	Patients			DLT	
		BC	NSCLC	Total	No.	Type
1	60/80	4	2	6	1	Grade 3 diarrhea
2	60/90	5	2	7	2	Grade 3 diarrhea, grade 4 neutropenia
3	70/90	5	3	8	2	Grade 4 diarrhea, grade 3 neutropenia day 15
4	70/100	6	4	10	3	Two grade 3 diarrhea, one grade 4 neutropenia
5	80/100	7	3	10	2	One grade 3 and one grade 4 diarrhea
Total		27	14	41	10	Seven diarrhea, three neutropenia

Six BC and four NSCLC patients were included at dose level 4 (DTX 70 mg/m^2 and CPT-11 100 mg/m^2). Overall, three DLTs occurred after the first cycle, but only one of these was observed in the first six patients enrolled. Grade 3 diarrhea was observed in two patients (one BC and one NSCLC), which did not require hospitalization, and grade 4 neutropenia in one patient.

At dose level 5 (DTX 80 mg/m^2 and CPT-11 100 mg/m^2), five BC and one NSCLC patient were initially treated. Two BC patients experienced severe diarrhea. One woman had to be hospitalized. In view of that we decided to suspend the dose escalation and to expand this cohort in order to obtain a more accurate estimation of the toxicity. An additional four patients (two BC and two NSCLC) were treated at the same doses. No additional DLTs occurred in these patients. In view of these findings this dose level was considered feasible and recommendable for phase II.

Treatment compliance and toxicity

All the 41 patients were assessed for toxicity. WHO hematologic and non-hematologic toxicities are listed in Table 3. No toxic deaths occurred. A mild cholinergic syndrome was observed in one patient during cycle 4.

Table 3 Toxicity in all 218 delivered cycles

Toxicity	WHO grade	
	1/2 Pts. (%)	3/4 Pts. (%)
Neutropenia	23 (57)	14 (34)
Thrombocytopenia	12 (30)	5 (12)
Anemia	26 (64)	3 (7)
Emesis	25 (61)	5 (12)
Diarrhea	18 (43)	9 (23)
Fatigue	25 (62)	8 (20)
Conjunctivitis	11 (27)	1 (3)
Skin toxicity	8 (20)	4 (10.5)
Alopecia	25 (61)	12 (30)
Hepatic	9 (23)	–
Neurologic	6 (15)	–

Only two patients (with BC) discontinued treatment because of toxicity. One patient complained of severe fatigue after six cycles and refused to continue chemotherapy. Another patient had to interrupt chemotherapy after three cycles because of the occurrence of severe thrombophlebitis. Overall, in 29 patients (70%) doses had to be reduced, and the actually delivered relative dose intensity was 78% of that planned for both drugs.

Considering all 218 cycles delivered, grade 3 or more neutropenia and thrombocytopenia occurred in 14 patients (34%) and 5 patients (12%), respectively. One patient had neutropenic sepsis requiring hospitalization. Red blood cell transfusions were required in 3 patients (7%). Fatigue and diarrhea were the most common non-hematologic side effects. They occurred at least once during treatment in 33 patients (82%) and 27 patients (66%), respectively, and were severe in 8 patients (20%) and 9 patients (23%). There was evidence of cumulative toxicity with regard to fatigue, which was severe in only two patients during the first four cycles. Diarrhea did not appear to be cumulative. Six of the nine patients who showed severe diarrhea during treatment had it during the first cycle, and in all nine patients it happened for the first time during the first four cycles. Nausea and vomiting were also frequent, occurring in 30 patients (73%) overall, but only in 5 (12%) was it severe. As a consequence of loss of appetite, vomiting and/or diarrhea, a $< 10\%$ weight loss was observed in 11 patients.

Conjunctivitis and skin toxicity were also frequently reported by patients. Severe skin toxicity consisted of palmar-plantar erythrodysthesia and was observed in four patients (10.5%). It partially reversed after dose reduction. Conjunctivitis occurred in a total of 12 patients (30%), being severe in one of them. Symptomatic cardiac toxicity was never observed, although in one patient the left ventricular ejection fraction decreased to a value $< 50\%$. A transient increase in liver enzymes, in the absence of liver localizations, was observed in nine patients (23%). Mild fluid retention occurred in three patients (7%). Alopecia was almost universal being of grade 3/4 in 12 patients (30%). A higher risk of grade 3/4 neutropenia (55%) and fatigue (31%) occurrence was observed in PS 2 patients.

Table 4 Response

Tumor	Evaluated	CR	PR	NC	PD	ORR (%)	Median duration (range) in months
Breast cancer	27	3	13	5	6	59	6 (3–13)
NSCLC	14	1	4	3	6	36	4 (2–9)
Total	41	4	17	8	12	51	5 (2–13)

Response

All 41 (27 BC and 14 NSCLC) enrolled patients were evaluable for response at the time of the present analysis (Table 4). A total of 21 objective responses were registered (ORR 51% [95% CI 35–67]). Three complete and 13 partial responses were registered in the 27 BC patients for a 59% ORR [95% CI 39–78]. An additional five patients showed SD. Two of the three patients with a CR had multiple liver localizations, and one had multiple lung nodules together with pleural effusion. Two of these CR patients were enrolled in this study after a short-lasting response to a previous cisplatin-epirubicin-paclitaxel (PET) regimen, and the other had not responded to both first and second-line chemotherapy. The three CRs lasted 4, 8 and 11 months, respectively. Overall, the median duration of response was 6 months (range 3–13 months). Responses according to previous treatment are shown in Table 5.

Five of the 14 NSCLC patients achieved a major response for a 36% ORR [95% CI 13–64]. One patient attained a CR. He had stage IV disease for multiple lung localizations and pleural effusion. Previous treatments consisted of three cycles of cisplatin-gemcitabine-vinorelbine which yielded SD, and six cycles of XR-5000 producing a partial response lasting 3 months. This patient achieved a CR after four cycles of DTX/CPT-11 treatment, which was confirmed after eight cycles. The patient was still relapse-free 8 months after the documentation of CR. An additional three NSCLC patients showed SD lasting 2, 3, 5 months, respectively.

Table 6 details the antitumor activity according to dose level. Antitumor activity was observed at all dose levels, and complete responses were also observed in the first cohorts. At a median follow-up of 16 months (range 10–23 months), 23 deaths had occurred (13 in BC and 10 in NSCLC patients). Median survival had not been reached at the time of this report in BC patients (projected 1-year survival being 75%), while it was 10 months in NSCLC patients.

Table 5 Response rate according to response to previous treatment

Tumor	Sensitive (response lasting >3 months)	Refractory (response lasting <3 months or no response)	Total
Breast	12/17 (70%)	4/10 (40%)	16/27 (59%)
NSCLC	3/5 (60%)	2/9 (22%)	5/14 (36%)
Total	15/22 (68%)	6/19 (32%)	21/41 (51%)

Discussion

The objectives of this dose-escalation study were to determine the MTD, the DLT, and the recommended doses of DTX and CPT-11 when given together every 2 weeks with filgrastim support in pretreated patients with advanced BC or NSCLC. At the time the study was designed, there was limited experience with this combination. The routine use of filgrastim was not planned in any of the published studies, and an every-2-week schedule was never adopted. Our choice of an every-2-week schedule was based on the hypothesis that a shorter interval between cycles could avoid tumor regrowth and consequently result in a higher antitumor activity (dose-dense approach). Moreover, we thought that the combined exposure of tumor cells to both drugs could maximize their synergism. However, the high incidence of severe neutropenia reported previously suggested the routine use of filgrastim [1, 5, 14, 18]. Since this was supposed to be a quite aggressive regimen, patients older than 70 years were excluded. Indeed, it was a standard policy in our institution to design specific trials for elderly cancer patients.

The doses of DTX and CPT-11 were safely escalated to 80 mg/m^2 and 100 mg/m^2 every 2 weeks. Overall, ten patients were treated at this dose level, with only two episodes of DLT after the first cycle. Therefore, we can consider these dosages as feasible and recommendable for future studies. We decided to stop the dose escalation at this level, although the rate of DLT observed did not

Table 6 Response according to dose level

Dose level	DTX/CPT-11 (mg/m^2)	Patients			Response						Total
		BC	NSCLC	Total	BC			NSCLC			
					CR	PR	ORR (%)	CR	PR	ORR (%)	
1	60/80	4	2	6		2	50		1	50	3 (50%)
2	60/90	5	2	7	1	2	60	0	0	0	3 (43%)
3	70/90	5	3	8		3	60	1	0	33	4 (50%)
4	70/100	6	4	10	1	3	66		1	25	5 (50%)
5	80/100	7	3	10	1	3	57		2	66	6 (60%)
Total		27	14	41	3	13	59	1	4	36	21 (51%)

force us to do it, because both patients experiencing DLT during the first cycle suffered from severe diarrhea (grade 4 in one case), and we were worried that a further dose escalation could have resulted in an unacceptable rate of severe diarrhea, which may sometimes be lethal. Indeed, severe diarrhea was the main troublesome side effect in this trial, representing the DLT in seven of ten cases and occurring in 23% of patients during their entire time on treatment. Diarrhea is expected to be the most frequent non-hematologic side effect of CPT-11 given every other week [24]. In previous experience at our institution with CPT-11 combined with 5-FU/folinic acid, diarrhea was the most troublesome toxicity, but much higher CPT-11 doses were delivered every 2 weeks [4]. The DTX dose used in the present study could also have played a role in increasing the occurrence of severe diarrhea. Severe diarrhea was also relevant in a Japanese study [18], although much lower doses of both drugs were delivered (DTX 50 mg/m^2 day 2 plus CPT-11 60 mg/m^2 days 1, 8 and 15 every 4 weeks).

Although in previous studies no pharmacokinetic interactions have been found between these two drugs [5, 18], it should be remembered that both drugs are metabolized in the liver. DTX is primarily metabolized by hepatic cytochrome P450 3A4 and 3A5 to its hydroxylation product (RPR 104952) [29]. CPT-11 is hydrolysed by carboxylesterase to SN-38, a compound that in vitro inhibits topoisomerase I at least 200 times more potently than its parent compound. The activity of the enzyme is primarily found in the liver, gastrointestinal tract epithelium, and tumor tissue. Most of the resulting SN-38 is conjugated by uridine diphosphate-glucuronyl transferase and is excreted into the bile as a glucuronide conjugate [10, 11, 13, 30]. A possible explanation for the apparently non-dose-dependent occurrence of diarrhea could have been genetic variability in carboxylesterase expression and/or activity, as variations in SN-38 levels have been observed between individuals for a given dose of CPT-11 [21].

A comment is merited regarding the dose intensity of the two drugs obtained in our every-2-week schedule. The DTX dose intensity delivered at the recommended dose (40 mg/m^2/week) was, beyond any doubt, very high, and even higher than that achieved when DTX is administered alone every 3 weeks in chemonaive patients. In previous trials testing the DTX/CPT-11 regimen, the recommended DTX dose every 3 or 4 weeks did not exceed 50–65 mg/m^2 [1, 5, 14, 18]. The routine use of filgrastim support played a major role in allowing such a high dose intensity to be delivered.

The CPT-11 dose intensity achieved in the present study does not appear particularly high. In a French study [5], a CPT-11 dose of 275 mg/m^2 together with DTX 60 mg/m^2 every 3 weeks seemed safe (although the authors recommended a CPT-11 dose of 250 mg/m^2 for future trials). However, the criteria for defining a DLT were a bit different from those used by us, because grade 4 neutropenia lasting 7 days or more (rather than 3 days or more) was considered a DLT. As a consequence, in the previous study 85% of patients had grade 3/4 neutropenia, and 22.5% neutropenic fever. In a Finnish study [14], the recommended CPT-11 dose every 3 weeks was 190 mg/m^2 (together with DTX 60 mg/m^2). In that study the incidence of either severe neutropenia or diarrhea was also very high, with 7 of 15 patients suffering from neutropenic fever, and 6 of 15 from grade 3/4 diarrhea. In an American trial [1], the recommended CPT-11 dose every 3 weeks was even lower (160 mg/m^2), although a much lower DTX dose intensity was delivered (65 mg/m^2 every 3 weeks).

Some preliminary observations concerning the antitumor activity can also be made, although the small number of patients enrolled (especially those with NSCLC) prevents us from drawing definite conclusions. It is interesting that 5 of the 14 NSCLC patients achieved a major tumor regression. In three of them full-dose paclitaxel had been given in first-line. The ORR (36%) we observed is similar to that reported by Japanese authors with this combination in chemonaive patients (37%) [18]. In a study of CPT-11 130 mg/m^2 plus docetaxel 50 mg/m^2 every 3 weeks in pretreated NSCLC patients, the confirmed ORR was 11%, with a median survival time of 7.4 months [25]. Single-agent DTX has shown activity in pretreated NSCLC patients. However, the ORR was only around 10% in the two reported randomized trials [6, 20]. The ORR and median survival observed in the present trial are, in our opinion, very appealing if we take into consideration that a relevant proportion of patients had poor prognostic parameters at the beginning of treatment (ECOG performance status 2, brain metastases) and that all patients had received an aggressive platin-based first-line treatment (in many cases also including paclitaxel).

The use of this combination in heavily pretreated BC patients had never been tested before. The promising ORR (59%) and survival observed were absolutely unexpected. We must consider that the chance of response in BC patients refractory to both anthracyclines and paclitaxel is very low [15, 26, 31]. Moreover, a relevant proportion of patients had received even a second-line treatment for advanced disease. The high DTX dose intensity obtained may be a possible explanation for this result. In a previous trial we tested DTX 40 mg/m^2 on days 1 and 8 every 3 weeks in combination with gemcitabine or vinorelbine and observed a much less-promising ORR [7]. It is difficult to define the role of CPT-11 in producing such a high antitumor activity. There are conflicting data on this subject. In a Japanese trial, only 5% of patients pretreated with doxorubicin and DTX responded to single-agent weekly CPT-11. However, the median total dose delivered was 388 mg/m^2 [28]. In another Japanese study, CPT-11 was administered weekly to 12 heavily pretreated breast cancer patients (all anthracycline-resistant). One CR and two PRs were achieved, with a median survival of 354 days [9]. In any case, the evidence of a very high ORR, and of a promising survival figure permit us to conclude that this regimen may rescue even patients who

have previously received a high dose intensity of paclitaxel and epirubicin.

In conclusion, the DTX plus CPT-11 every-2-weeks regimen, with filgrastim support, is a safe approach in refractory BC and NSCLC patients. This regimen has promising activity in both these populations. Therefore, phase II trials testing this combination in pretreated BC and NSCLC are ongoing.

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