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ORIGINAL ARTICLE

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A phase I–II study of bi-weekly gemcitabine and irinotecan as second-line chemotherapy in non-small cell lung cancer after prior taxane + platinum-based regimens

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Abstract *Purpose*: Treatment options in patients with recurrent non-small cell lung cancer (NSCLC) remain limited as a result of poor activity of most agents after failure of platinum-based therapy. In the present phase I–II study, we evaluated the feasibility and efficacy of bi-weekly gemcitabine (GEM) + irinotecan (CPT-11) in patients with relapsed NSCLC. *Patients and methods*: Patients with advanced NSCLC, WHO-performance status (PS) ≤ 2, prior taxane/platinum-based chemotherapy were eligible. Chemotherapy was administered in a dose-escalated fashion in subgroups of 3–6 patients until dose-limiting toxicity (DLT) was encountered as follows: CPT-11 150 or 180 mg/m^2 followed by GEM 1,200–1,800 mg/m^2, both on days 1 + 15, recycled every 28 days in four dose levels (DLs). *Results*: Forty-nine patients entered the phase I and II part of the study (phase I: 12–phase II: 37 + 3 at DL-3), and 40 patients were evaluable for a response in phase II and all for toxicity: median age, 61 years (range 36–74); PS, 1 (0–2); gender, 43 males/6 females—histologies; adenocarcinoma, 25; squamous, 20; large cell, 4. Metastatic sites included lymph nodes, 38; bone, 5; liver, 4; brain, 3; lung nodules, 14; adrenals, 13; other, 3. All patients had prior taxane + platinum-based treatment, and 42 patients had prior docetaxel–ifosfamide–cisplatin/or–carboplatin regimens. DLT was observed at DL-4 and included 2/3 cases with grade 3 diarrhea—1/3 of these with febrile neutropenia. The recommended DL for phase II evaluation was DL3: GEM, 1,500 + CPT-11—180 mg/m^2. Objective responses in phase II were PR, 6/40 [15%; 95% confidence interval (CI), 5–31%]; stable disease, 16/40 (40%; 95% CI, 21–53%); and progressive disease, 18/40 (45%; 95% CI, 28.5–62.5%). The median time-to-progression was 4 months (range 1–12) and median survival 7 months (range 1.5–42 +), while 1-year survival was 20%. Grade 3/4 neutropenia was seen in 18% of patients (6% grade 4) and 6% incidence of febrile neutropenia. No Grade 3/4 thrombocytopenia were seen, grade 3 diarrhea in 6% of patients and grade 2 in 15% of patients, while other grade 3 non-hematologic toxicities were never encountered. *Conclusions*: Bi-weekly GEM + CPT-11 is active and well tolerated in patients with advanced NSCLC failing prior taxane + platinum regimens, and represents an effective and convenient combination to apply in the palliative treatment of relapsed NSCLC particularly after failure of first-line docetaxel + platinum-based regimens.

Keywords Gemcitabine · Irinotecan · Phase I · Chemotherapy · Lung cancer

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Introduction

Despite significant improvements in the management of advanced (stages IIIB/IV) non-small cell lung cancer (NSCLC), the vast majority of patients will develop progressive disease (PD). Treatment options regarding second-line chemotherapy have been limited so far and no data were available until 2000 demonstrating the benefit of chemotherapeutic agents in treating relapsed/refractory disease over best supportive care (BSC) alone, when the study of Shepherd et al. [1] was reported demonstrating a significant advantage of single-agent docetaxel versus BSC in both survival and quality of life [1]. Additionally, another randomized 3-arm study comparing single-agent docetaxel 100 or 75 mg/m^2 every 3 weeks versus vinorelbine (VNR) 30 mg/m^2/week versus ifosfamide 6 g/m^2 (divided over 3 days)/3 weeks in platinum-pretreated patients with relapsed NSCLC demonstrated 1% RR among 245 patients allocated to single-agent ifosfamide or VNR arm, while a prolonged median time-to-progression (TTP) and survival were observed for single-agent docetaxel [2]. Therefore, the above two large multi-institutional phase III randomized studies [1, 2] established docetaxel as the recommended treatment choice in the salvage setting of NSCLC after platinum-based first-line treatment.

Recently, the introduction of several newer cytotoxic agents, such as gemcitabine (GEM), VNR and Paclitaxel, with demonstrated activity in NSCLC has resulted in improved outcome with first-line treatment incorporating these agents in combination with platinum drugs. More specifically, GEM, a deoxycytidine analogue with pyrimidine antimetabolite activity, has demonstrated improved survival when combined with cisplatin versus cisplatin alone [3], while it has demonstrated satisfactory single-agent activity as second-line treatment in NSCLC [4–6].

Irinotecan (CPT-11) is a semisynthetic chemotherapeutic agent derived from the natural alkaloid camptothecin and belongs to topoisomerase-I interactive compounds [7, 8]. CPT-11 demonstrated a broad spectrum of efficacy against various solid tumors and lack of cross-resistance and synergistic antitumor activity with GEM in patients with advanced/metastatic pancreatic cancer and NSCLC [9, 10]. The combination of CPT-11 and GEM has demonstrated to have synergistic effects in vitro on the SCOG small-cell lung cancer (SCLC) cell line, which provides an experimental basis for conducting clinical trials using these agents [11]. Moreover, phase I studies have demonstrated the feasibility of combining GEM + CPT-11 (IrinoGem) administered at 1,000 and 100 mg/m^2 (both on days 1 + 8), respectively, in patients with advanced pancreatic cancer and NSCLC [12].

On the basis of the synergistic antitumor activity with distinct mechanisms of action but without any anticipated major overlapping toxicity, we conducted this phase I–II study of bi-weekly GEM + CPT-11 regimen, in order to evaluate the efficacy and toxicity profile in patients with advanced NSCLC who had progressed after prior taxane + platinum-based combinations, in particular in patients who have been exposed to first-line docetaxel + platinum-based chemotherapy, and are therefore not candidates for the widely approved at present salvage chemotherapy with single-agent docetaxel.

Patients and methods

Patient selection

Patients with histologically confirmed advanced NSCLC, stages IIIA/IIIB and IV, that had relapsed after or progressed on a taxane + platinum-based combination chemotherapy regimen and had never received GEM and camptothecin analogues (CPT-11 or topotecan) were candidates for the present study. Eligibility included: (1) histologically confirmed NSCLC in relapse not potentially curable by surgery and or radiotherapy, (2) WHO performance status (PS) ≤ 2, (3) life expectancy ≥ 3 months, (4) adequate hematopoietic [absolute neutrophil count (ANC) $> 1{,}500/\mu l$, platelet count (PLT) $> 100{,}000/\mu l$], liver [bilirubin < 1.5 mg/dl, AST/ALT $< 2\times$ upper normal limit (nl), unless caused by tumor and serum albumin > 3.0 g/dl] and renal function (BUN and creatinine < 1.5 nl; nl $= 1.5$ mg/dl in our laboratory or creatinine clearance > 50 ml/min), (5) progression after or during prior chemotherapy with a taxane + platinum analogue-based regimen; docetaxel–ifosfamide–cisplatin (DIP) [13], docetaxel–ifosfamide–carboplatin (DICb) [14], docetaxel–carboplatin, paclitaxel–carboplatin, and paclitaxel–ifosfamide–cisplatin (PIC) [15], (6) absence of active coronary artery disease (in the form of unstable angina or myocardial infarction over the last 12 months), unstable diabetes mellitus, or peripheral neuropathy $\geq$ grade 2 by the NCI-common toxicity criteria (CTC), (7) no prior irradiation to areas encompassing $> 30\%$ of marrow-bearing bone, apart for emergency radiotherapy for superior vena cava obstruction, imminent vertebral or weight-bearing long bone fracture as a result of metastatic involvement, or symptomatic rapidly progressive brain metastases and (8) presence of bi-dimensionally measurable with or without evaluable disease sites (however, all patients had to have at least one bi-dimentionally measurable lesion) located outside a previously irradiated field, unless definite evidence of progression at this site was documented. The study was approved according to Institutional policies and informed consent obtained from each patient before study entry.

Treatment schedule

Eligible patients (Table 1) were entered at the dose levels (DLs) of the CPT-11 + GEM combination as shown in Table 2. Both drugs, CPT-11 plus GEM, were administered on the same day every 2 weeks (days 1 + 15) and recycled every 4 weeks. CPT-11 was administered at a

dose of 150–180 mg/m^2 as a 60-min intravenous infusion followed by GEM at a dose of 1,200–1,800 mg/m^2 as a 30-min intravenous infusion (Table 3). Antiemetics were administered before chemotherapy with 24 mg of ondasetron or 3 mg of granisetron combined with 20 mg of dexamethasone on the day of treatment. No subsequent antiemetic drug doses were planned unless the patient experienced nausea or vomiting, in which case he was instructed to take additional per os doses of ondasetron 8 mg t.i.d or granisetron 1 mg q.d until nausea/vomiting resolved, usually for 1–2 days post-chemotherapy. Cholinergic symptoms that occurred during or shortly after CPT-11 infusion were treated with subcutaneous (s.c.) atropine 0.5–1 mg. Loperamide tablets were administered in order to reduce the severity of delayed ($>$ 24 h) diarrhea. Patients were instructed to begin taking loperamide 2 mg with the first loose stool followed by 2 mg every 2 h irrespectively of whether they had another episode until they remained without any episode of diarrhea for at least 12 h. During the night, patients were instructed to receive 4 mg of loperamide every 4 h.

Table 1 Patient characteristics

Characteristics	Number	Percentage
Total patients	49	100.0
Sex		
Male	43	87.8
Female	6	12.2
Age (years)		
Median 61 (range 36–74)		
Performance status (WHO)		
0	12	25
1	30	61
2	7	14
Stage at initial diagnosis		
IIIB	15	31
IV	34	69
Histology		
Squamous	25	51
Adenocarcinoma	20	41
Large cell/unspecified	4	8
Prior non-medical therapy		
Surgery	4	8
Radiotherapy	11	22
Previous first-line chemotherapy		
Docetaxel/ifosfamide/cisplatin	17	35
Docetaxel/ifosfamide/carboplatin	25	51
Docetaxel/carboplatin	3	6
Docetaxel/ifosfamide/cisplatin	2	4
Paclitaxel/carboplatin	2	4
Metastatic sites at relapse		
Liver	4	8
Bone	5	10
Brain	3	6
Lung nodules	14	29
Adrenals	13	27
Pleural effusion	5	10
Lymph nodes	38	78
Other	3	6
Number of metastatic sites		
1	17	35
2 or $>$	32	65

Table 2 GEM + CPT11 dose levels in the phase I part of the study

Dose level	Drug doses		Number of patients entered
	Irinotecan (mg/m^2)	Gemcitabine (mg/m^2)	
1	150	1,200	3
2	150	1,500	3
3	180	1,500	3 + 37 (phase II)
4	180	1,800	3

Table 3 Results of GEM + CPT11 dose escalation in phase I

DL	Number of patients	Number of treatment cycles	DLT	Types of toxicity (grades 3 and 4)
1	3	13	0/3	None
2	3	18	0/3	None
3	3	14	0/3	None
4	3	10	2/3	2 Gr 3 diarrhea, 1 of these Gr 4 neutropenia (+ FN)

DL dose level, *DLT* dose-limiting toxicity (after 1st cycle), *FN* febrile neutropenia

Supportive care

Prophylactic administration of hematopoietic growth factors either granulocyte-colony stimulating factor (G-CSF) or recombinant human erythropoietin (rh-Epo) were not allowed during phase I. Patients who entered the phase I part of the study after the first two cycles as well as patients entered in phase II were allowed to continue with prophylactic G-CSF administration 5 μg/kg s.c./day, days 3–7 or until WBC $\geq$ 5,000 per μl in the case of grade 4 neutropenia in previous cycles. Recombinant human erythropoietin (rh-Epo) was administered at 10,000 IU s.c. t.i.w (not on chemotherapy days) whenever a drop of hemoglobin (Hb) $\leq$ 10.5 g/dl was seen and continued until Hb $\geq$ 12 g/dl.

Dose escalation schedule , DLTs and dose modifications

Dose-limiting toxicities (DLTs) were assessed during the first chemotherapy cycle and were considered to have been reached when one of the following was met: (1) grade 4 neutropenia, (2) any episode of febrile $\geq$ grade 3 neutropenia, (3) any episode of grade 4 thrombocytopenia, (4) any non-hematologic grade 3 or 4 toxicity excluding nausea/vomiting, musculoskeletal-arthritic pain and alopecia.

Cohorts of three patients were entered at the DLs shown in Table 2. In the case that DLT was encountered (defined above) in 1/3 patients at a certain DL, a total of six patients were entered at that particular level and if $>$ 2/6 (33%) met the DLT requirements (in total at least 3/6 patients developed the same DLT) no further accrual to the next higher DL was undertaken and the level immediately before the DLT was considered as the MTD. In the case that two out of the first three patients

at a certain level experienced the same DLT, no more patients were accrued at that level and further dose-escalation was stopped. The DL immediately before the one that DLT was reached, i.e., the MTD, was recommended for further phase II testing.

The prerequisites for dose modifications were set as follows: (1) any episode of grade 4 neutropenia, (2) any episode of febrile $\geq$ grade 3 neutropenia, (3) any episode of grade 4 thrombocytopenia, (4) any non-hematologic grade 3 or 4 toxicity excluding nausea and vomiting, flu-like illness and alopecia.

The following guidelines were applied with respect to dose reductions for toxicity: (1) For neutropenia, meeting the aforementioned criteria, both GEM and CPT-11 doses were reduced by 20% in subsequent cycles and if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles treatment was stopped; however, the patient was evaluable for toxicity and response. (2) For grade 4 thrombocytopenia, reduction of GEM and CPT-11 by 20% was applied as specified for neutropenia. (3) For $\geq$ grade 3 mucositis, the doses of GEM and CPT-11 were reduced by 20% in subsequent cycles. (4) For $\geq$ grade 3 diarrhea, the dose of CPT-11 was reduced by 20% in subsequent cycles.

In the case that blood counts had not recovered to ANC $\geq$ 1,500 per μl and PLT $\geq$ 100,000 per μl on day 1 of therapy, treatment was withheld until recovery, and after a maximum delay of 2 weeks no further therapy was administered in case that counts did not return to normal. In the case of ANC = 1,000–1,500/μl and/or PLT = 75,000–100,000 per μl on day 15, both drugs were given after a 20% dose reduction. Whenever ANC $\leq$ 1,000/μl and/or PLT $\leq$ 75,000 on day 15, no treatment was given on that day and subsequent doses were reduced by 20% for both drugs throughout treatment.

Pretreatment, follow-up studies and response evaluation

Tumor measurements were performed by physical examination and the specific radiological test that documented measurable disease before treatment. Clinical examination, full blood counts, biochemical tests, appropriate serum tumor marker measurements and a chest X-ray were carried out before each cycle of therapy. Blood counts were checked on the days of treatment (day 1 + 15) and weekly thereafter or every 3 days in the case of neutropenia until full recovery. Evaluation of response was performed every two cycles of therapy with CT scans of the chest, abdomen, or the radiological examinations that detected disease in other sites. Patients experiencing toxic death despite objective responses at measurable sites would be categorized as treatment failures. Complete remission (CR) is defined as the disappearance of all signs and symptoms of disease for at least 1 month, with the documented disappearance of all known lesions by physical examination, X-rays, CT scans, bone scans, and the development of no new lesions. Partial remission (PR) indicates a decrease of 50% or greater (compared with pre-treatment measurements) in the sum of the products of the two largest perpendicular diameters of all measurable lesions and no concomitant growth of new lesions for at least 1 month (confirmation after 1 month was required for all responders). There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. Stable disease (SD) indicates a decrease of less than 50% or an increase in tumor size less than 25% over the original measurements. There could be no deterioration of symptoms or performance status unless secondary to drug toxicity. PD was defined as an increase of 25% or greater over the original measurements in the sum of the products of the two largest perpendicular diameters of any measurable lesions, and relapse was defined as occurring following a period of response when a former lesion reappeared or enlarged as above or a new lesion appeared. Full staging evaluation had to be performed, as reported above, before treatment initiation. Follow-up disease evaluation was performed at approximately 3-month intervals after the end of treatment.

Quality of life evaluation

Quality of life (QoL) was evaluated in patients during the phase II portion of the present study ($n = 40$) by analyzing a ten-item questionnaire derived from the Lung Cancer Symptom Scale [16]. Patients were requested to complete the questionnaire before starting treatment, after three and six treatment cycles and every 3 months thereafter until death. The QoL questionnaire consisted of the five most frequent disease-related symptoms (cough, appetite loss, dyspnea, fatigue, and pain) and another five-item section concerning psychologic, social, emotional aspects and general well being.

Statistical methods

Patients who received at least two cycles of treatment were evaluable for response and patients who received at least one cycle of treatment were evaluable for toxicity. Response duration was measured from the day of its initial documentation until confirmed disease progression; TTP was calculated from study entry until evidence of PD; overall survival was measured from the day of entry until last follow-up or death. Actuarial survival was estimated by the product-limit method of Kaplan and Meier [17].

According to Simon's two-stage mini–max design for phase II studies [18], a sample of 40 patients (in phase II), has approximately 80% power to accept the hypothesis that the true RR is $> 20\%$, while 5% significance to reject the hypothesis that the true RR is $< 10\%$, if less than four responses occur. At the first stage if less than two responses occur out of the first 21 patients, the study will conclude that the anticipated RR is $< 10\%$ and terminate. Thereby, the probability of accepting a therapy with a real response rate less than 10% and the risk of rejecting a treatment with a response rate greater than 20% would be in both the cases less than 10%.

Results

Patient characteristics

The study was conducted between June 2001 and October 2004. Forty-nine patients were entered and their characteristics are shown in Table 1, and 12 were treated in phase I DLs (DL1, 3; DL2, 3; DL3, 3; and DL4, 3) and the remaining 37 at DL3, which was defined as the level for further phase II testing (phase I: 12–phase II: 37 + 3 at DL3) (see also Table 2). In total, 40 patients were treated at DL3 (GEM 1,500 mg/m^2+ CPT-11 180 mg/m^2), which was defined as the MTD (see below) (Table 3). All patients received at least two cycles of chemotherapy and were therefore evaluable for response and toxicity.

Toxicities

Phase I Four DLs were evaluable for toxicity in the phase I part of the current study. No DLTs were observed at DL1, DL2, and DL3. At DL4 2/3 initial patients entered developed grade 3 diarrhea, while one of these patients developed FN concurrently with the diarrheic episodes after the first chemotherapy cycle. Both were managed successfully with hydration, broad spectrum antibiotics (for FN), and other appropriate supportive measures. Therefore, neither further accrual of patients was undertaken nor further dose escalation beyond DL4 was attempted according to our preset definitions. No other important hematologic or non-hematologic grade 3/4 dose-limiting toxicities were observed in the phase I part of the study (Table 3).

Phase II Hematologic and non-hematologic toxicities encountered in the present study were evaluated in all patients and administered cycles and are shown in Tables 4 and 5, respectively. In brief, grade 3/4 neutropenia was seen in 7/40 (18%) of patients—2/40 (5%) of patients with grade 4, while 2/40 (5%) of patients developed FN. Both were managed successfully with broad spectrum antibiotics in the outpatient setting with amoxicillin/clavulanate plus ciprofloxacin. No grade 3/4 thrombocytopenia was seen, while anemia grade 3 developed in 2/40 (5%) and grade 2 in 3/40 (7.5%) of patients.

Grade 3 diarrhea was seen in 3/40 (7.5%) of patients, while 6/40 (15%) patients developed grade 2 diarrhea, that was successfully managed with intensive loperamide therapy and s.c. octreotide as required. Other grade 3 non-hematologic toxicities were never encountered.

Grade 1, acute cholinergic symptoms (acute diarrhea, abdominal cramps, etc.) were seen in 6/40 patients (15%) during or shortly after CPT-11 administration, and all cases were managed successfully with s.c. atropine 0.5–1.0 mg, that was administered as pre-emptive therapy in subsequent cycles before CPT-11. Grade 2 alopecia was seen in 18/40 (45%), grade 1–2 asthenia/fatigue in 10/40 (25%), grade 1-2 nausea/vomiting in 8/40 (20%), grade 1 GEM-related pyrexia in 2/40 (5%), grade 1 edema in 2/40 (5%) and grade 1 pulmonary toxicity in 1/40 (2.5%) patients. No treatment-related deaths were observed in either the phase I or phase II parts of the present study.

Table 4 Hematologic toxicities (NCI-CTC grade) of GEM + CPT-11 regimen

Toxicity	NCI-CTC grade (percentage of patients, all cycles)				
	0	1	2	3	4
Leukopenia	10	30	12.5	12.5	5
Neutropenia	15	50	17.5	12.5	5
Thrombocytopenia	80	15	5	0	0
Anemia	77.5	10	7.5	5	0
Febrile neutropenia	5				

Table 5 Non-hematologic toxicities (NCI-CTC grade) of GEM + CPT-11 regimen

Toxicity	NCI-CTC grade (percentage of patients, all cycles)				
	0	1	2	3	4
Nausea and vomiting	80	15	5	0	0
Diarrhea	57.5	20	15	7.5	–
Mucositis	92.5	7.5	0	0	0
Acute cholinergic	85	15	0	0	0
Alopecia	0	55	45	0	–
Hepatic	90	10	0	0	–
Asthenia/fatigue	75	15	10	0	–
Pulmonary	97.5	2.5	0	0	0
Flulike syndrome	95	5	0	–	–
Peripheral edema	95	5	0	–	–
Peripheral neuropathy	0	0	0	0	0
Cutaneous rash	92.5	7.5	0	0	0

Compliance to treatment

In the phase I part of the study, the initial 2/3 patients entered at DL4, that developed DLTs continued with 20% dose reduction in subsequent cycles, while the third patient did not require dose reduction.

A total of 189 treatment cycles were administered (phase II); median 4 (range 2–6), with a mean of 4.7 cycles per patient. Sixteen patients did not complete the planned six cycles due to the following reasons: PD, 18 patients (10 after cycle 2, and 8 after cycle 4), SD with persisting severe symptoms necessitating palliative radiotherapy; 3 patients, and personal choice; 2 patients after cycle 4, while 1 patient with SD elected not to receive the cycle 6. Ten treatment cycles (5.3%) were delayed for 7–14 days for the following reasons: patient's own choice or logistic reasons related to admission; four cycles, transfusion for anemia; four cycles, and thrombocytopenia on the day of treatment; two cycles.

Dose-intensity analysis

The administered mean dose-intensities for each drug of the GEM/CPT-11 combination in the phase II part of the study were as follows: for GEM 690 mg/m^2/week (range 650–750) or 92%, and for CPT-11 80 mg/m^2/week (range 75–90), or 88.8%. However, the administered median dose-intensities for each drug of the GEM/CPT-11 combination in phase II were similar to the planned dose-intensities: GEM, 750 mg/m^2/week; CPT-11, 90 mg/m^2/week.

Response to treatment and survival

In total, 48 out of the 49 patients entered were evaluable for response when both phase I and II parts of the study (all DLs) were considered. Overall, seven PRs were recorded, for a 14.3% (95% CI, 4.5–24%) RR on an intent-to-treat basis.

Objective responses in phase II were as follows: PR, 6/40 [15%; 95% confidence interval (CI), 5–31%]; SD, 16/40 (40%; 95% CI, 21–53%); and PD, 18/40 (45%; 95% CI, 28.5–62.5%). The median TTP was 4 months (range 1–12 months) and median survival 7 months (range 1.5–42 + months), while 1-year survival was 20%. The one patient surviving > 42 months post-chemotherapy (with GEM + CPT-11), received gefitinib p.o. on a compassionate need protocol after failure of second-line chemotherapy.

The QoL score improved in 16/32 (50%) of patients that could be evaluated; in particular, cough, appetite loss, dyspnea, fatigue, and pain improved in 56, 40, 59, 47, and 53% of patients, respectively. Six out of 16 patients (37.5%) who experienced a QoL improvement had achieved a PR to treatment.

Discussion

As an increasing proportion of patients with advanced NSCLC derive clinical benefit and prolonged survival with novel drug–platinum combinations, such as paclitaxel/carboplatin, docetaxel/cisplatin or carboplatin, VNR/cisplatin and GEM/cisplatin or carboplatin, it is anticipated that many of these patients will require some type of salvage chemotherapy after relapse or disease progression. Based on the past experience, such an option was rather limited given that response rates were low with platinum-based first-line regimens, and PS was rather poor [19]. Therefore, the RR≥14%, that we observed in the present study with GEM/CPT-11 as second-line treatment in advanced NSCLC, appears adequately encouraging in this setting.

Until recently, the only cytotoxic agent approved in the salvage treatment of NSCLC, after failure of first-line platinum-based therapy, was docetaxel based on the results of the two large multi-institutional phase III randomized studies [1, 2]. Recently, a multi-targeted antifolate (MTA) agent named pemetrexed has shown equivalence to single-agent docetaxel in the second-line treatment of NSCLC, in terms of RR, TTP, and OS, whereas its toxicity profile and QoL were more favorable compared to docetaxel [20]. However, these data were not available when the present phase II study was initiated, and there is no information whether pemetrexed has any activity after docetaxel-based first-line treatment. Moreover, the kind of treatment most suitable after failure of first-line docetaxel/platinum-based therapy is currently unknown and not supported by any phase III data, while it appears reasonable to administer drugs that have different mechanisms of action, such as GEM, CPT-11 or topotecan, and VNR.

The present phase I/II study was designed on the basis that both GEM and CPT-11 represent two of the most active single agents in advanced NSCLC [4–8]. Moreover, the combination of GEM and CPT-11 has been demonstrated to have synergistic activity against SCLC cell lines, which provides the experimental background for conducting clinical trials applying these agents in lung cancer [11]. GEM (2′,2′-difluoro-2′-deoxycytidine) is a nucleoside analogue and its cytotoxicity has been correlated with incorporation into genomic DNA and concomitant inhibition of DNA synthesis. In an in vitro experimental model, incorporation of GEM was found to induce topoisomerase I cleavage complexes into DNA. Based on these findings, the investigators concluded that the enhancement of camptothecin-induced topoisomerase I cleavage complexes might, at least in part, contribute to the synergistic or additive effects of GEM in combination with Topotecan or CPT-11 in human breast and lung cancer cell lines [21].

The combination of GEM and CPT-11 has been investigated as first and second-line treatment in advanced NSCLC, as well as in phase I–II studies in patients with advanced pancreatic cancer and various refractory solid tumors [9, 22–24]. The schedule of drug administration has been variable, with most studies applying a day 1 + 8 regimen for both drugs (recycled every 21 days), or a GEM day 1 + 8—CPT-11 day 8, or less often a day 1 + 15 regimen for both drugs.

Kakolyris et al. [23], conducted a phase I dose-escalation study of GEM 900–1,200 mg/m^2 days 1 + 8 and CPT-11 200–350 mg/m^2 day 8, in 27 patients with advanced NSCLC failing after a docetaxel/cisplatin regimen, and between 23 evaluable patients reported a RR of 4.5%, SD 52.5% and median OS 9 months, while the recommended doses for further phase II evaluation were 1,000 mg/m^2 for GEM on days 1 + 8 and 300 mg/m^2 for CPT-11 on day 8 with a quite limited and acceptable toxicity profile [23]. Similarly, a low toxicity profile of the regimen was further verified in three phase I studies [22, 24, 25]. In the first study, GEM + CPT-11 were both administered weekly ×3 consecutive weeks-1 week rest in 30 patients with advanced-refractory solid tumors [22] and resulted in a 30% incidence of grade 3/4 neutropenia and 10% diarrhea, while the recommended doses for further phase II evaluation were GEM 1,000 mg/m^2 and CPT-11 60 mg/m^2. In the other two studies, the recom-

mended doses for the combination, both given on days 1 + 8 every 3 weeks, were GEM 1,000 mg/m^2 and CPT-11 100 mg/m^2 [24, 25]. In the Japanese phase I study, enrolling 12 patients, the objective RR was 16.6% [25].

Based on the results of the phase I study by Kakolyris et al. [23], a phase II randomized trial was conducted by the same group in NSCLC patients, who had failed prior docetaxel/cisplatin, evaluating the combination of GEM/CPT-11 (at the doses recommended in phase I) compared to single-agent CPT-11 (300 mg/m^2/3 weeks) [26]. The combination of GEM/CPT-11 resulted in a higher RR (18.4 vs. 4.2%) and better control of disease-related symptoms than CPT-11 alone, but without any survival improvement. More cycles had to be delayed and required prophylactic G-CSF support with GEM/CPT-11, whereas 11.3 vs. 3.9% of patients in the GEM/CPT-11 and CPT-11 groups, respectively, developed FN ($P = 0.09$) and one patient died of sepsis in each group.

Three recent studies, a phase I and two phase II studies, were the first ones to evaluate the combination of GEM/CPT-11 both administered on a bi-weekly schedule. The phase I study by Nishio et al. [27] evaluated a fixed dose of GEM 1,000 mg/m^2 combined with escalated doses of CPT-11 starting at 50 and escalated up to 150 mg/m^2, the recommended dose as single agent in Japan. Some DLTs were observed at the last DL, with 3/9 patients developing grade 3 diarrhea and grade 1 neutropenia/diarrhea precluding cycle completion on day 15, but based on the generally good tolerability and compliance without cumulative toxicity, the authors recommended GEM 1,000 mg/m^2 + CPT-11 150 mg/m^2 on a bi-weekly schedule (day 1 + 15) for further phase II testing. A further ongoing phase II study conducted by the same investigators applying the doses recommended in phase I, between 22 assessable patients a 18.5% RR and a 35% 1-year OS were reported with negligible toxicity [28].

The other study was a direct phase II evaluation of GEM 1,800 mg/m^2 + CPT-11 150 mg/m^2 on days 1 + 15 leading to a 16% overall RR and 36% 1-year survival [29]. Drug doses were chosen rather arbitrarily, and not based on any previous phase I evaluation. However, the regimen proved feasible with a 14% incidence of grade 3/4 neutropenia, and 6% grade 3 diarrhea, but 10% of the patients enrolled developed FN, which is considered rather high in the palliative setting. In contrast, the present phase I/II study defined that drug doses could not be escalated beyond DL-5 (GEM 1,800 mg/m^2 + CPT-11 180 mg/m^2), as dose-limiting diarrhea and neutropenia were observed in the first 2/3 patients. The difference in the tolerable doses between the present study and the study of Pectasides et al. [29] might be attributed to the fact that, according to the predefined dose-escalation schedule, we did never test GEM 1,800 mg/m^2 with CPT-11 at 150 but at 180 mg/m^2. Another possible explanation, for the inability to further escalate drug doses in the present study as a result of dose-limiting diarrhea, is that patients at DL-5 might have had poor compliance to the strict protocol of high-dose loperamide for managing late-onset diarrhea associated with CPT-11. Moreover, in the absence of other phase I data at these drug doses, the fact that dose-limiting diarrhea was observed when attempting to escalate GEM and keep constant the dose of CPT-11 was rather unexpected. One can argue that above a certain DL, GEM might enhance CPT-11's toxicity on bowel mucosa, either through synergistic/additive activity, or some form of pharmacokinetic interaction leading to increased levels of the active CPT-11 metabolites. However, to add further to the discussion regarding MTDs of the bi-weekly GEM + CPT-11, one has to stress-out another phase II study of that combination conducted in relapsed/refractory SCLC applying GEM: 2,000 mg/m^2+ CPT-11: 175 mg/m^2 [30]. The regimen proved extremely well tolerated with 9% grade 3/4 neutropenia (1 FN) and no episodes of grade 3 diarrhea.

The results of our study are in accordance to previous studies and confirm that the GEM + CPT-11 combination is safe, with an efficacy similar to that yielded by other phase II studies in relapsed NSCLC. Efficacy figures in the present study compare favorably to single-agent GEM, docetaxel, and VNR, but somewhat inferior to those obtained in previous studies of our group in this setting with GEM + VNR and GEM + docetaxel [31–33]. However, it should be pointed-out that the latter studies had incorporated a higher number of patients that were initially diagnosed at earlier disease stages (IIIA-N2/IIIB) and had obtained prolonged remissions to front-line chemotherapy, in contrast to the present study where most patients were stage IIIB (with malignant pleural effusion) or IV at initial diagnosis and were treated with docetaxel + platinum-based regimens [14]. In addition, measures important in the palliative setting of second-line therapy in relapsed/refractory NSCLC, such as symptomatic benefit response and QoL were adequately met in the present study; improvement of dyspnea, cough reduction, weight loss, PS, and pain were observed in 40–59% of cases. Despite the rather modest overall RR 15%, treatment was associated with a 20% 1-year survival.

In conclusion, the combination of GEM + CPT-11 administered on a bi-weekly schedule, at the doses defined in the present phase I–II study, in patients with advanced NSCLC failing after first-line chemotherapy (mainly docetaxel + platinum), appears to be active, with an acceptable toxicity profile, convenient and effective in controlling disease-related symptoms. Randomized comparisons to acceptable second-line alternatives; single-agent pemetrexed, or other active combinations in this setting are therefore warranted.

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