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Phase-I-study of four different schedules of pemetrexed, gemcitabine and cisplatin in patients with locally advanced or metastatic solid tumours ☆

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ABSTRACT

This non-randomised Phase-I-study determined recommended dose (RD) and dose-limiting toxicities (DLTs) of four different schedules combining pemetrexed (P), gemcitabine (G) and cisplatin (C). Patients ⩾18 years with locally advanced/metastatic cancer were enrolled. Doses were escalated for one 21-d (q3w; PGC d1, G d8) and three 28-d schedules (q4wA: PG d1, GC d15; q4wB: GC d1, PC d15; q4wC: PGC d1+15). Starting doses were P 400/500 mg/m^2 (q3w/q4w), G 800 mg/m^2 and C 40 mg/m^2. Sixty patients were enroled (n = 12/14/30/4 for q3w/q4wA/q4wB/q4wC). Common cancers included head and neck (n = 19), prostate (n = 7), sarcoma (n = 5) and stomach (n = 5). Thirteen patients experienced DLTs, most frequently fatigue (n = 4) and neutropenia (n = 3). Schedule q4wB reached the highest doses (P 600 mg/m^2 d15; G 1250 mg/m^2 d1; C 70 mg/m^{2}d1+15). There were no CRs, 11 PRs and 25 SDs (n = 47). The PGC-combination was feasible. The recommended schedule for subsequent studies would be 1250 mg/m^2 G and 60 mg/m^2 C on d1, followed by 500 mg/m^2 P and 60 mg/m^2 C on d15.

1. Introduction

Pemetrexed (LY232514 Alimta®; Eli Lilly, Indianapolis, IN) is a multitargeted antifolate that inhibits the biosynthesis of pyrimidine and purine nucleotides through inhibition of multiple folate-dependent enzymes, including thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase.[1] In Phase-I-trials, pemetrexed doses of 500–600 mg/m^2 administered every 21 d (q3w) were generally well tolerated.[2]

Pemetrexed has shown broad clinical antitumour activity in colorectal, pancreatic and breast cancer and is approved worldwide for the treatment of malignant pleural mesothelioma (MPM) and non-small cell lung cancer (NSCLC).[1,3] Toxic-

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ities are generally mild. Myelosuppression, skin rash and mucositis are major toxicities, neutropenia is the primary dose-limiting toxicity (DLT).[4,5]

Combining pemetrexed (P) with gemcitabine (G) and cisplatin (C) may achieve synergistic effects by combining different mechanisms of action and overlapping spectra of clinical efficacy. Synergy of PG, GC and PC-doublets was seen in cancer cell lines and animal models;[6–10] no such data are available for PGC triplet combinations. In clinical studies, the PC doublet combination (500 mg/m^2 d1, 75 mg/m^2 d1, q3w) achieved response rates of 39–45% in advanced NSCLC and of 41–46% in MPM.[11–13] Toxicities of doublet regimens were sufficiently low as to consider the development of PGC triplet or sequential doublet combinations feasible. Platinum-based triplets yielded controversial results in NSCLC patients.[14–16] However, none of these triplets included the new agent pemetrexed.

Therefore, this Phase-I-dose-finding study was designed to determine the maximum-tolerated dose (MTD) and the recommended dose (RD) and schedule of PGC-combination treatment in patients with locally advanced or metastatic solid tumours. Initially, a q3w-triplet schedule was evaluated, with PGC on d1 followed by G only on d8. However, a similar Phase-I-study with PG on d1 and G on d8 showed that the d8 G dose was associated with considerable toxicity.[17] Thereafter, Phase-II-studies indicated that G was less toxic when given on d1+15 than on d1+8.[18–21] We thus extended our study to explore three alternative four-week (q4w) schedules, a triplet and two sequential doublets, with drugs administered on d1+15.

2. Patients and methods

2.1. Patients

Male or female patients (⩾18 years) with histologically or cytologically confirmed locally advanced or metastatic solid tumours were enrolled. Additional eligibility criteria included predicted life expectancy of ⩾12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and adequate haematopoietic, hepatic and renal function; no more than two previous chemotherapeutic regimens. Prior radiation to <25% of bone marrow was allowed if completed ⩾30 d before study entry. Patients with symptomatic CNS-metastases or serious concomitant systemic disorder were excluded.

2.2. Study design

This single-centre, non-randomised Phase-I-dose-escalation study was conducted at the St. Georg Hospital in Hamburg, Germany, to assess the feasibility of PGC-combination treatment in patients with solid tumours. The protocol was approved by the institutional review board, and all subjects gave informed consent. The primary objective was to determine the maximum-tolerated dose (MTD), secondary objectives included evaluation of dose-limiting toxicities (DLTs), establishing a recommended dose (RD, a dose-level lower than the MTD) and a schedule for subsequent studies, as well as collection of anecdotal information on antitumour activity.

Initially, one q3w-triplet schedule of PGC was escalated, using starting doses approximately 20% below the standard doses for single-agent treatment: P 400 mg/m^2, G 800 mg/m^2, C 40 mg/m^2 on d1; plus G 800 mg/m^2 on d8. After new studies indicated that q4w-schedules might be less toxic,[16–19] dose escalation was stopped for this q3w-triplet. Three alternative q4w-schedules were then escalated in parallel; two sequential doublets: (A) GP d1, GC d15; (B) GC d1, PC d15; and one triplet: (C) PGC d1+15. Starting doses for all q4w-schedules were P 500 mg/m^2, G 800 mg/m^2 and C 40 mg/m^2, corresponding to the highest dose-level evaluated for the q3w-schedule. P was administered as 10 min, G as 30 min and C as 2 h intravenous infusion in all schedules. If given, P was always administered first, followed by G; C was administered last.

Each patient received up to six cycles of the assigned schedule and dose-level (no within-patient dose escalation). Dose reductions in subsequent cycles were not allowed, cycles had to be delayed up to 42 d in case of relevant toxicities. Treatment was discontinued in case of intolerable toxicity or disease progression.

All patients had to take daily oral folic acid (350–600 μg/d) and received intramuscular injections of 1000 μg cyanocobalamine (vitamin B_{12}) 1–2 weeks before the first dose of pemetrexed and every 9 weeks thereafter. Oral dexamethasone 4 mg (or equivalent corticosteroid) was to be taken twice daily on the day before, of and after each administration of pemetrexed.

Patient enrolment for all three alternative schedules proceeded concurrently (non-randomised).

Any of the following events during the initial treatment cycle was considered a DLT and required patient discontinuation: CTC Grade 4 (G4) neutropenia $<0.5\times10^9$/l lasting ⩾7 d or febrile neutropenia (fever ⩾38.5 °C and neutropenia $<1.0\times10^9$/l); G3 thrombocytopenia with bleeding requiring platelet transfusion, or any G4 thrombocytopenia; G ⩾ 3 non-haematological toxicity (except alopecia, inadequately treated nausea/vomiting and skin toxicity responding to local or systemic therapy); any toxicity prohibiting re-treatment on d22 (q3w-schedule) or causing treatment delay or omission of the d15 dose (q4w-schedules), which would require discontinuation of study treatment.

Dose-escalation proceeded similarly in all schedules, considering potential cumulative toxic effects occurring after multiple cycles. Only 1 agent was escalated per dose-level, in steps of +100 mg/m^2 for P, +200 or +250 mg/m^2 for G and +10 mg/m^2 for C (Table 2 presents actual dose-levels).

A minimum of 3 patients were studied per dose-level. If none experienced a DLT, the subsequent 3 patients were enroled at the next higher dose-level. If 1 of 3 patients experienced a DLT, up to 3 more patients were treated at the same level. When the *same* DLT was observed in ⩾2 patients of the 6 patients, the MTD was reached and dose-escalation stopped for this schedule. The recommended dose (RD) for future studies was established as a dose-level lower than the MTD, additionally considering any potential cumulative toxic effects identified after multiple cycles of the PGC combination.

2.3. Baseline and treatment assessments

Patient history, concomitant medication and performance status were obtained before study entry and with each treat-

ment cycle. Haematological laboratory parameters were assessed weekly, non-haematological laboratory assessments and physical examinations prior to each chemotherapy dose. In patients with measurable disease, antitumour activity was evaluated according to RECIST criteria.[20] Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (CTC; version 2.0).

3. Results

3.1. Patient characteristics

Sixty patients with locally advanced (30%) or metastatic (70%) solid tumours were enroled into one of the four different treatment schedules (n = 12/14/30/4 into Schedules q3w/A/B/C). All but 1 patient enroled were Caucasian (59, 98.3%), median ages ranged from 47 years in Schedule q4w C to 66 years in Schedule A (range, 29–78 years). Overall, 48 patients were male (80%), with the majority of patients being male in each schedule. The most common tumour types were head and neck cancers in 19 patients (31.7%), followed by prostate cancer in 7 patients (11.7%), and sarcoma and stomach cancer in 5 patients each (8.3%). Patients receiving prior therapy included 23 patients (38.3%) with prior systemic therapy (chemo- or hormonal therapy); of these, 20 patients had prior chemotherapy (13× one, 7× two prior lines). Prior radiation was reported for 26 patients (43.3%) and prior surgery for 36 patients (60.0%). Details are shown in Table 1.

3.2. Treatment schedules and patient disposition

Of the 60 patients enrolled, only 9 (15%) completed the maximum six cycles of any of the four different PGC schedules. These included 3 patients on the q3w-triplet and 5 on Schedule B, but only 1 patient on Schedule A and none on the q4w-triplet Schedule C. Most common reasons for discontin-

Table 1 – Patient characteristics (all patients, n = 60)

	Schedule q3w PGC d1, G d8 (n = 12)	Schedule q4w A GP d1, GC d15 (n = 14)	Schedule q4w B GC d1, PC d15 (n = 30)	Schedule q4w C PGC d1, PGC d15 (n = 4)
Age (years)				
Median	58	66	63.5	47
Range	38–77	29–73	36–78	43–73
Sex (n)				
Male/female	9/3	13/1	22/8	4/0
ECOG PS (n)				
0/1/2	2/10/0	2/6/6	12/14/4	0/4/0
Tumour type (n)				
Head and neck cancer	6	6[a]	6[b]	1
Prostate cancer	1	1	4[c]	1[d]
Sarcoma	0	0	4	1
Stomach cancer	0	2	3	0
CUP	2	1	1	0
NSCLC	0	0	4	0
Mesothelioma	0	1	3	0
Oesophageal cancer	0	1	2	0
Renal carcinoma	1	1	1	0
Thymoma	1	0	0	1
Bladder cancer	0	0	1	0
Cholangiocarcinoma	1	0	0	0
Colon cancer	0	0	1	0
Liver cancer	0	1	0	0
Disease stage (n)				
Locally advanced/metastatic	8/4	5/9	5/25	0/4
Prior systemic therapy				
Yes/no	5/7	5/9	11/19	2/2
Prior radiation				
Yes/no	6/6	9/5	10/20	1/3
Prior surgery				
Yes/no	5/7	10/4	19/11	2/2

Abbreviations: P, pemetrexed; G, gemcitabine; C, cisplatin; q3w, every 3 weeks; q4w, every 4 weeks; ECOG PS, ECOG performance status; NSCLC, non-small cell lung cancer; CUP, cancer of unknown primary origin.

a 1 patient had second primary malignancy (head and neck + CUP).

b 1 patient had second primary malignancy (head and neck + oesophageal cancer).

c 3 patients had second primary malignancies (prostate + CUP, prostate + bladder, prostate + NSCLC + CUP).

d Patient had second primary malignancy (prostate + urothelial cancer).

uation were non-fatal adverse events ($n = 25$, 41.7%) and progressive disease ($n = 15$, 25.0%).

Table 2 presents the dose-levels used and the number of patients exposed to each dose-level. The q4w-schedule B was escalated to the highest dose-level. Discontinuation rates for this schedule were 69.2% (9/13) in dose-levels 1–4, but 94.1% (16/17) in dose-levels 5–8. On the three highest dose-levels of Schedule B, no patient completed 6 cycles of treatment.

3.3. *Dose administration*

Overall, 190 cycles were administered (44/33/102/11 cycles for schedules q3w/A/B/C). The median number of cycles was highest (3.0, ranges 1–6) for Schedule B, intermediate (2.5, ranges 1–6) for Schedule q3w and lowest (2.0) for Schedules A and C (ranges 1–4). For the q3w-schedule, 4 dose reductions were reported in 3 patients (25.0%), all due to Grade 3/4 neutropenia. No dose reductions were allowed in the q4w-schedules. Dose (64) delays were reported in 37 of 46 patients who received more than one treatment cycle. Of all 64 delays, 48 were due to clinical reasons (q3w 8 delays, Schedule A 7 delays, Schedule B 29 delays, Schedule C 4 delays). Overall, 25 dose omissions on d8 (q3w) or d15 (q4w) were reported in 20 of 60 patients (33.3%): in 5/12 patients (41.7%), 3/14 patients (21.4%), 10/30 patients (33.3%) and 2/4 patients (50.0%) for Schedules q3w, A–C respectively. In addition, 1 patient on

Table 2 – Treatment schedules, dose-levels and dose-limiting toxicities

Schedule	Dose-level	Dose (mg/m^2, d)			Number of patients exposed	Dose-limiting toxicities (Number of patients)
		Pemetrexed (P)	Gemcitabine (G)	Cisplatin (C)		
q3w: PGC day 1, G day 8	1[a]	400, d1	800, d1+8	40, d1	6	G3 skin toxicity (1)[a] Febrile neutropenia (1)[a]
	2[a]	500, d1	800, d1+8	40, d1	6	G3 syncope (1) G3 diarrhoea (1)
q4w A: GP day 1, GC day 15	1	500, d1	800, d1+15	40, d15	3	None
	2	500, d1	1000, d1+15	40, d15	4[b]	None
	3 (MTD)	500, d1	1000, d1+15	50, d15	7[b]	G3 thrombocytopenia with omission of day 15 dose (1) Fatal pancytopenia including G3 thrombocytopenia requiring transfusions, G4 neutropenia, non-haematological G3/4 toxicities (1)[d] G2 transaminase elevation with omission of day 15 dose (1) G2 fever requiring dose delay on day 15 (1)
q4w B: GC day 1, PC day 15	1	500, d15	800, d1	40, d1+15	3	None
	2	500, d15	1000, d1	40, d1+15	4[b]	None
	3	500, d15	1000, d1	50, d1+15	3	None
	4	500, d15	1250, d1	50, d1+15	3	None
	5	500, d15	1250, d1	60, d1+15	4[c]	None
	6	500, d15	1250, d1	70, d1+15	3	None
	7 (MTD)	600, d15	1250, d1	70, d1+15	3	G2 decreased creatinine clearance with omission of day 15 dose (1) G2 decreased creatinine clearance with omission of day 15 dose and CTC grade 3 fatigue (1)
	8	600, d15	1250, d1	60, d1+15	7[b]	G3 fatigue and G3 syncope (1)
q4w C: PGC day 1, PGC day 15	1 (MTD)	500, d1+15	800, d1+15	40, d1+15	4	G3 fatigue and G4 neutropenia with dose delay on day 15 (1) G3 fatigue and G3 syncope (1)

Abbreviations: P, pemetrexed; G, gemcitabine; C, cisplatin; q3w, every 3 weeks; q4w, every 4 weeks; d, day of treatment cycle; DLT, dose-limiting toxicity; MTD, maximum-tolerated dose (reached if 2 identical DLTs occurred during initial cycle); NCI-CTC, National Cancer Institute, Common Toxicity Criteria version 2.0; G1, Grade 1; G2, Grade 2; G3, Grade 3.

a MTD formally not reached (DLTs during initial cycle were not identical), but schedule discontinued due to publication data suggesting that q4w-schedules were less toxic.

b DLT was not evaluable in 1 patient, therefore 1 additional patient was recruited on this dose-level.

c One additional patient enroled on dose-level 5 of Schedule q4w B for ethical reasons.

d Left heart failure identified as cause of death in a post-study autopsy report.

dose-level 8 of Schedule B discontinued cisplatin from cycle 4 onwards due to non-haematological toxicity, but continued GP because he had benefit from therapy.

3.4. *MTD, RD and study treatment discontinuation*

The MTD was defined as the dose-level at which 2 or more of up to 6 patients experienced the same DLT during the initial treatment cycle, and was identified separately for each schedule. The RD was defined as a dose-level lower than the MTD, additionally considering any cumulative toxicities identified after multiple treatment cycles. Overall, 13 patients experienced DLTs (first cycle only) and were thus discontinued from study treatment. Fatigue (4 patients) and neutropenia (2 patients G 4; 1 patient febrile neutropenia) were the most frequent DLTs, followed by syncope, thrombocytopenia and decreased creatinine clearance requiring treatment discontinuation (2 patients each; Table 2).

For the q3w-triplet, dose escalation was stopped on the second dose-level without meeting formal MTD-criteria. The q4w-triplet C (PGC given biweekly) was not escalated, 2 patients experienced 4 DLTs on the initial dose-level. For the sequential doublets, the MTD for Schedule A (GP day 1, GC day 15) was reached on dose-level 3 (Table 2). Schedule B (GC day 1, PC day 15) was escalated to the highest dose-level, with 2 identical DLTs (creatinine clearance decreased) occurring at dose-level 7, thus the MTD was reached at 600 mg/m^2 P, 1250 mg/m^2 G and 70 mg/m^2 C. The 2 DLTs observed – decreased creatinine clearance – were considered as typical cisplatin-specific toxicities. The cisplatin dose for subsequent studies of Schedule B was thus recommended to be 60 mg/m^2. An attempt to further escalate the pemetrexed dose using the lower cisplatin dose of 60 mg/m^2 and a pemetrexed dose of 600 mg/m^2 (dose-level 8) was not feasible, because there was one DLT (fatigue and syncope) and a high rate of required dose omissions and delays in the following cycles. Thus, the RD for future studies was established to be 1250 mg/m^2 G and 60 mg/m^2 C on d1, followed by 500 mg/m^2 and 60 mg/m^2 C on d15.

3.5. *Haematological and non-haematological toxicity*

Table 3 summarises all NCI-CTC G3/4 toxicities by treatment schedule. For each schedule, neutropenia was the most frequent haematological toxicity. Rates of patients with G3/4 neutropenia ranged between 64.3% (Schedule A) and 83.3% (q3w-schedule). G3/4 thrombocytopenia rates were highest for the q3w-schedule (66.7%) and low for all 3 q4w-schedules (0–14.3%, G3 only). G3 febrile neutropenia was reported in 2 patients of the q3w-schedule, but in none of the other schedules.

In Schedule B, the following G3/4 haematological toxicity rates were observed: neutropenia 73.3%, thrombocytopenia 10.0% and anaemia 13.3%. Toxicities were in a similar fre-

Table 3 – Summary of maximum Grades 3 and 4 haematological and non-haematological toxicities (all patients, n = 60)

Type of toxicity	Schedule q3w PGC d1, G d8 (*n* = 12)		Schedule q4w A GP d1, GC d15 (*n* = 14)		Schedule q4w B GC d1, PC d15 (*n* = 30)		Schedule q4w C PGC d1, PGC d15 (*n* = 14)	
	G3 *n* (%)	G4 *n* (%)	G3 *n* (%)	G4 *n* (%)	G3 *n* (%)	G4 *n* (%)	G3 *n* (%)	G4 *n* (%)
Haematological								
Neutropenia	1 (8.3)	9 (75.0)	0	9 (64.3)	8 (26.7)	14 (46.7)	2 (50.0)	1 (25.0)
Leucopenia	4 (33.3)	6 (50.0)	2 (14.3)	8 (57.1)	12 (40.0)	3 (10.0)	1 (25.0)	1 (25.0)
Thrombocytopenia	6 (50.0)	2 (16.7)	2 (14.3)	0	3 (10.0)	0	0	0
Anaemia	3 (25.0)	0	5 (35.7)	0	2 (6.7)	2 (6.7)	1 (25.0)	0
Non-haematological								
Fatigue	1 (8.3)	1 (8.3)	3 (21.4)	0	2 (6.7)	0	4 (13.3)	0
Diarrhoea	3 (25.0)	0	1 (7.1)	0	0	0	0	0
Syncope	1 (8.3)	0	0	0	1 (3.3)	0	1 (25.0)	0
Rash	1 (8.3)	0	1 (7.1)	0	1 (3.3)	0	0	0
Anorexia	1 (8.3)	0	0	0	0	0	0	0
Dehydration	1 (8.3)	0	0	0	0	0	0	0
Headache	1 (8.3)	0	0	0	0	0	0	0
Hypocalcaemia	0	0	1 (7.1)	0	0	0	0	0
Hypokalaemia	0	0	1 (7.1)	0	1 (3.3)	0	0	0
Hypomagnesaemia	0	0	0	0	1 (3.3)	0	0	0
Hyponatraemia	1 (8.3)	0	0	0	1 (3.3)	0	0	0
Nausea	1 (8.3)	0	0	0	0	0	0	0
Odynophagia	0	0	0	0	1 (3.3)	0	0	0
Peripheral ischaemia	0	0	0	0	1 (3.3)	0	0	0
Pneumonia	0	0	1 (7.1)	0	0	0	0	0
Stomatitis	0	1 (8.3)	0	1 (7.1)	0	0	0	0
Vomiting	1 (8.3)	0	0	0	1 (3.3)	0	0	0

Note: Data are presented as number (%) of patients with maximum toxicity. Toxicity grades were rated according to NCI-CTC toxicity grading, version 2.0.

Abbreviations: P, pemetrexed; G, gemcitabine; C, cisplatin; q3w, every 3 weeks; q4w, every 4 weeks; d, day of treatment cycle; NCI-CTC, National Cancer Institute, Common Toxicity Criteria; G1, Grade 1; G2, Grade 2; G3, Grade 3; G4, Grade 4.

quency range across dose-levels, there was no pronounced increase of haematological toxicities.

No laboratory non-haematological G3/4 toxicities were reported. G4 non-laboratory toxicities were reported in 2 patients on the q3w-schedule (1× fatigue, 1× stomatitis) and 1 on Schedule A (stomatitis); none occurred with Schedules B and C. The most frequent G3 non-haematological toxicities were fatigue in 10 patients (16.7%), diarrhoea in 4 patients (6.7%) and syncope and rash in 3 patients each (5.0%).

Three patients died during treatment; 6 additional patients died within 30 d of last treatment. The investigator rated one death as due to study drug toxicity (neutropenia and anaemia; Schedule A, dose-level 3); however, left heart failure was identified as the cause of death for this patient in a subsequent autopsy report. All other deaths were due to study disease or other non-drug-related causes.

3.6. *Tumour response*

47 patients were evaluable for tumour response (had measurable disease and completed at least one cycle) according to RECIST criteria. There was no complete response (CR), 10 patients achieved confirmed partial response (PR) there was 1 additional unconfirmed PR. Stable disease (SD) was reported in 25 patients, 5 patients had progressive disease (PD) and response was rated unknown in 6 patients. Table 4 summarises tumour response by treatment schedule. High proportions of patients achieved either PR or SD: 72.7%, 66.7%, 83.3% and 66.7% in Schedules q3w, A, B and C, respectively. The 10 confirmed PRs were achieved in the following tumour types: NSCLC (2), head and neck cancer (2), prostate cancer and second primary malignancy (2; second malignancies of bladder cancer and cancer of unknown primary origin [CUP]), mesothelioma (1), oesophageal cancer (1), bladder cancer (1) and CUP (1). In Schedule B, 3 PRs occurred on dose-level 8, and 1 PR each on dose-levels 2–7.

4. Discussion

Doublet pemetrexed (P) and gemcitabine (G) combinations have been assessed in Phase-I- and II-studies in different tumour entities including NSCLC,[17,22–26] breast cancer,[27] urothelial cancer[28] and a variety of solid tumours.[29] Most trials used 21 d (q3w) schedules, with G 1250 mg/m^2 on d1+8, and P 500 mg/m^2 given either on d1 or d8. A large, randomised Phase-II-trial of three different schedules identified P followed by G on d1, with G only given on d8, as the most efficacious and least toxic sequence for advanced NSCLC.[30] This regimen achieved a confirmed response rate of 31%, median survival of 11.4 months and median time to progression of 4.7 months. Administration of P on d8 rather than on d1 (immediately after G) did not seem to negatively impact the therapeutic index of first-line treatment in NSCLC patients.[25]

Our study was the first to evaluate combination treatment with pemetrexed, gemcitabine and cisplatin (PGC) in patients with a variety of solid tumours. The initial q3w-triplet, PGC on d1 and G only on d8, was feasible. But dose escalation was stopped at P 500 mg/m^2, G 800 mg/m^2 and C 40 mg/m^2 in favour of 3 alternative q4w-schedules, one triplet and 2 sequential doublets, because additional data suggested that drug administration on d1+15 may be less toxic.[17–21] More recent studies in patients with a variety of solid tumours have now shown that the PG doublet, administered on d1+15, is well tolerated and shows antitumour activity.[31–33]

In our study, the corresponding triplet of PGC given on d1+15 (Schedule C) was not feasible; dose escalation had to be stopped at the first, low dose-level of P 500 mg/m^2, G 800 mg/m^2 and C 40 mg/m^2. However, the 2 sequential doublet schedules were feasible: Schedule A (GP d1, GC d15) was escalated up to P 500 mg/m^2, G 1000 mg/m^2 and C 50 mg/m^2; Schedule B (GC d1, PC d15) up to a higher dose of P 600 mg/m^2, G 1250 mg/m^2 and C 70 mg/m^2. Grade 3/4 neutropenia was the most frequent haematological toxicity, with similar rates in all regimens, ranging between 64% (q4wA) and 83% (q3w) of patients. Schedule B thus reached the highest dose-level and was well tolerated (Grade 3/4 haematological toxicity rates: neutropenia 73%, anaemia 13% and thrombocytopenia 10%). There were no toxicity-related deaths, no events of febrile neutropenia and non-haematological toxicity was rare.

Regarding antitumour activity, response rates were 9.1% for the q3w-triplet (1× PR) and 37.5% (9× PR) for the sequential doublet Schedule B. No CRs or confirmed PRs were observed with Schedules A and C. High proportions of patients achieved SD or PR, e.g. 83% on Schedule B and 73% on the q3w-triplet. These antitumour activities were in a similar

Table 4 – Antitumour activity (evaluable patients, n = 47)

	Schedule q3w PGC d1, G d8 (*n* = 11)	Schedule q4w A GP d1, GC d15 (*n* = 9)	Schedule q4w B GC d1, PC d15 (*n* = 24)	Schedule q4w C PGC d1, PGC d15 (*n* = 3)
Tumour response, n (%)				
Complete response	0	0	0	0
Partial response	1 (9.1)	1× unconf.	9 (37.5%)[a]	–
Stable disease	7 (63.5)	5 (55.6)	11 (45.8%)[b]	2 (66.7)
Progressive disease	1 (9.1)	1 (11.1)	2 (8.3%)[c]	1 (33.3)
Unknown	2 (18.2)	2 (22.2)	2 (8.3%)	–

Abbreviations: P, pemetrexed; G, gemcitabine; C, cisplatin; q3w, every 3 weeks; q4w, every 4 weeks; d, day; unconf., unconfirmed.

a 3 PRs on dose-level 3, 1 each on dose-levels 2–7.

b 2 SDs each on dose-levels 1,4,5,8; 1 SD each on dose-levels 2, 3, 6.

c 1 PD each on dose-levels 2 and 3.

range than seen with biweekly PG (without platinum) in 2 Phase-II-studies on first-line treatment in advanced NSCLC.[34,35] In both studies, P was given at the standard 500 mg/m^2 dose, G at a higher than standard dose of 1500 mg/m^2. Response rates of 20% (no CR; 95% CI 10–36%) and 28.3% (1 CR, 26.4% PR) were observed, with additional 54% and 45% of patients achieving SD. Haematological toxicities were also in a similar range than with PGC: G3/4 neutropenia 51% and 28%, febrile neutropenia 14% and 9%, anaemia 8% and none stated, thrombocytopenia 3% and 2%.

At least for NSCLC, addition of a third agent to standard doublet treatment has led to inconclusive results: In two studies, triplet treatment improved response rates, but not survival,[36,37] whereas another Phase-II/III-study concluded that the addition of G to paclitaxel/carboplatin combination treatment (triplet d1, G d8) offered a significant survival advantage over the doublet in advanced NSCLC.[38] Another recent meta-analysis concluded that addition of a third-generation cytotoxic agent to a platinum-based doublet was associated with improved response rate and survival, but increased haematological and neurological toxicity.[39] The authors suggested that triplet treatment may be considered in selected patients with good performance status.

In our study, the highest dose-levels were reached with sequential doublets rather than with triplet treatment. To date, only one other small Phase-I-study has evaluated a sequential doublet PGC combination, given as q4w-schedule.[40] In this study, 10 patients with metastatic transitional cell carcinoma of the urothelium received GC on d1 and PG on d15. The MTD (one dose-level above RD) was already reached at G 800 mg/m^2, P 400 mg/m^2 and C 60 mg/m^2. Two patients achieved an objective response (1 CR, 1 PR, 22.2%). These results are less favourable when compared to Schedule B evaluated in our study.

There is an ongoing discussion on the optimal sequence of administration when P and G are given on the same day. Preclinical data yielded inconclusive results.[7,41] Depending on the cancer cell lines used, synergistic cytotoxicity was either maximal when G was given first [17,42,43] or, in the majority of studies, when P was given first.[43–46] It was hypothesised that P given first might result in a cell cycle shift towards the S phase, thus potentially facilitating G activity.[43,44] In our study, P was administered immediately prior to G when both were given on the same day. Most previous clinical studies had included a 90-min interval before starting the second infusion, but a study by Treat and coworkers had indicated that this 90 min delay may not be required,[24] Sequence-dependent effects have also been discussed for GC combinations. In mice bearing NSCLC tumours, an almost 3-fold decrease of intrastrand platinum–DNA adducts occurred when G was given 4 or 24 h prior to C.[47] Crul and colleagues confirmed the possibility of this negative effect when G was given 1 d before C.[48] However, a more recent study in different cell lines confirmed that G increased intrastrand-platinum–DNA adduct formation if both drugs were given simultaneously.[49] In our study, G was given immediately prior to C in all 4 schedules evaluated. Further research would be needed to clarify if the schedules assessed could be optimised by modifying the GC administration sequence.

Our Phase-1-study has limitations: It was designed to identify the MTDs and RDs of 4 different treatment regimens in parallel, not to identify the treatment with the best benefit-risk ratio. The non-randomised patient accrual may have caused considerable bias and precludes any direct comparison between regimens. In particular, treatment groups differed in terms of tumour entities, age and performance status and thus may have differed in terms of response and tolerability. Also, survival was not an end-point in this Phase-I-study, and we did not perform any pharmacokinetic assessments. However, pharmacokinetics of GC combinations have extensively been studied in previous Phase-I-trials.[48,50,51] An effect of C on G pharmacokinetics could not be detected,[9] the effects of G on C have been discussed above. Pharmacokinetics of P are also well known,[52] and numerous pharmacokinetic analyses of pemetrexed in combination with other agents including cisplatin[5] and gemcitabine[17] have shown that their concomitant administration had no significant influence on the pharmacokinetics of either agent.

In conclusion, PGC-combination treatment was feasible; the recommended schedule for subsequent studies in diverse populations would be a sequential doublet of 1250 mg/m^2 G and 60 mg/m^2 C on d1, followed by 500 mg/m^2 P and 60 mg/m^2 C on d15. Currently, no further exploration is planned because other combinations, e.g. combinations including targeted agents, are generally considered of higher clinical interest.[53]

Conflict of interest statement

At the time the study was conducted, Axel-R. Hanauske, the principal investigator of the study, has consulted Eli Lilly and Company as scientific advisor; he received honoria and research grants from Lilly. He is now a Lilly employee. Henrik Depenbrock and Ute Ohnmacht are also Lilly employees.

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