Phase I trial of gemcitabine, doxorubicin and cisplatin (GAP) in patients with advanced solid tumors

Ignacio Duran[a], Lillian L. Siu[a], Eric X. Chen[a], Amit M. Oza[a], Jeremy Sturgeon[a], Soo F. Chin[a], Shirley Brown[a], Gregory R. Pond[a] and Michelle Nottage[a]

A phase I study was conducted to determine the recommended phase II dose, safety profile and anti-tumor activity of a combination regimen of gemcitabine, doxorubicin and cisplatin (GAP). Gemcitabine (G) and doxorubicin (A) were administered on days 1 and 8 at increasing doses (starting level 800 and 15 mg/m^2, respectively). Cisplatin (P) was given at a fixed dose of 50 mg/m^2 (day 1). Treatment cycles were repeated every 3 weeks. Nineteen patients received 76 cycles of treatment. A and G were escalated up to 20 and 1000 mg/m^2, and finally de-escalated to 15 and 800 mg/m^2. The dose-limiting toxicity was neutropenic fever that was observed in 21% of the patients. Non-hematological toxicities included mild/moderate nausea, vomiting, diarrhea and fatigue, observed in 58, 37, 21 and 95% of the patients, respectively. Of 19 patients with evaluable disease, six patients had a partial response yielding an overall response rate of 31.6 % (95% confidence interval 12.6–56.6%) by intention-to-treat. We conclude that GAP is an active and tolerable treatment combination, with minimal visceral organ toxicities. *Anti-Cancer Drugs* 17:81–87 © 2006 Lippincott Williams & Wilkins.

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[a]Princess Margaret Hospital, University Health Network, Department of Medical Oncology and Hematology, Toronto, Ontario, Canada.

Correspondence to L.L. Siu, Princess Margaret Hospital, University Health Network, Department of Medical Oncology and Hematology, 610 University Avenue, Suite 5-210,Toronto, Ontario M5G 2M9, Canada.
Tel: +1 416 946-2911; fax: +1 416 946-6546;
e-mail: lillian.siu@uhn.on.ca

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Introduction

Gemcitabine (G) is an anti-metabolite, nucleoside analog of deoxycytidine that interferes with DNA synthesis through inhibition of ribonucleotide reductase and competition with deoxycytidine triphosphate for incorporation into DNA. Doxorubicin (A) is an anthracycline antibiotic that induces DNA strand breakage through DNA intercalation, and inhibition of both topoisomerase II and DNA polymerase. Cisplatin (P) forms DNA adducts which would lead to cell death if they were not excised and repaired through unscheduled DNA synthesis. Combining these three drugs with non-overlapping cytotoxic mechanisms would theoretically result in additive or synergistic anti-tumor activity by interfering with DNA processing at multiple critical steps.

The GAP combination has not been previously reported as a triplet in the treatment of solid tumors or hematological malignancies. Pairs of these agents however, have been combined in different doublets showing anti-tumor efficacy. G and A were used in combination in a phase I/II trial on transitional cell carcinomas of the urothelial tract that demonstrated a good toxicity profile and promising activity. In this study, dose-limiting toxicity (DLT) was not reached at the highest dose level studied (G 2000 mg/m^2 and A 50 mg/m^2 every 2 weeks) and eight of 14 patients achieved a partial response (PR) [1]. A phase II study of the same combination in 18 patients with renal cell carcinoma reported two complete responses (CRs) and five PRs with no grade 4 toxicities [2]. Another phase I/II study combining these two drugs was conducted in 50 patients diagnosed with advanced hepatocellular carcinoma. Recommended doses of G 1250 mg/m^2 (days 1 and 8) and A 30 mg/m^2 (day 1) in 21-day cycles were reached in this study, which demonstrated modest activity with this doublet and an acceptable toxicity profile [3]. A and P have been combined in the treatment of endometrial carcinoma and sarcoma [4,5]. In endometrial carcinomas, combination doses are in the range of A 45–60 mg/m^2 plus P 50 mg/m^2 every 3 weeks, whereas in sarcomas the most commonly prescribed regimen includes higher doses of both drugs (A 75 mg/m^2 plus P 100 mg/m^2 3-weekly). The most significant treatment-related toxicities in both schemas have been myelosuppression, nausea and vomiting. The combination of weekly doses of G (800–1000 mg/m^2) plus 3- to 4-weekly P (70–100 mg/m^2) has been tested in non-small cell lung cancer with good efficacy and toxicity, thus representing one of the standard treatments for this tumor type [6,7]. The same doublet, with G administered at 1000 mg/m^2 on days 1, 8 and 15, and P at 70 mg/m^2 on day 2 every 4 weeks, is used currently as a standard regimen in metastatic bladder cancer [8]. Lastly, the combination of G, P and dexamethasone has demonstrated an overall response rate of 49% and acceptable toxicity in patients with

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recurrent or refractory non-Hodgkin's lymphoma [9], and is undergoing further evaluation in this disease site.

The primary objective of this phase I trial was to determine the recommended phase II dose (RPTD) and assess the toxicity profile of the triplet combination of GAP in patients with advanced solid tumors. Our hypothesis was that by combining these three cytotoxic agents of non-overlapping anti-tumor mechanisms and activity, this triplet would yield a regimen of good therapeutic index for multiple solid tumor types.

Patients and methods

Eligibility

Patients were required to have histologically or cytologically documented advanced solid tumors refractory to conventional therapy or for whom there are no standard therapies. Certain tumor types such as nasopharyngeal and gynecological cancers were targeted given the established activity of these chemotherapeutic agents.

Eligibility criteria also included the following: age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; measurable disease; adequate organ functions with an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, INR ≤ 2, AST/ALT $\leq 3 \times$ upper limit of normal (ULN), total serum bilirubin $\leq$ ULN and serum creatinine $\leq 1.25 \times$ ULN (or calculated creatinine clearance ≥ 60 ml/min); a baseline left ventricular ejection fraction $> 50\%$ by MUGA scan must be documented for patients with a history of coronary artery disease, congestive heart failure or hypertension; a negative pregnancy test for female patients with child-bearing potential (Table 1).

Radiotherapy was permitted, but must have been completed at least 4 weeks prior to study entry and not to sole site(s) of measurable disease unless there was documented progression of disease within the field. Patients must not have received cytotoxic therapy within 30 days of study entry with other experimental drugs or anticancer therapy. Prior chemotherapy including G or anthracyclines was not permitted. Prior P was allowed provided that residual ototoxicity or neuropathy was less than grade 2 by the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0. Patients with brain metastases were eligible if previously documented intracranial disease had been stable for over 3 months and were clinically asymptomatic. The study protocol was reviewed and approved by the Institutional Review Board of the Princess Margaret Hospital, University Health Network. All patients gave written informed consent before study entry.

Pretreatment evaluation

At study entry, baseline evaluations included complete medical history and physical examination, evaluation of previous toxicity, routine laboratory evaluations [complete blood counts (CBCs) with differential, biochemical profiles and coagulation], urinalysis, chest X-ray, ECG, MUGA scan (only for patients with a history of coronary artery disease, congestive heart failure or hypertension) and radiological imaging of assessable disease. CBCs with differential and biochemical profiles were performed on days 1 and 8 of every treatment cycle. CBCs with differential was then repeated on day 15 or on alternate days until resolved if grade 4 neutropenia or thrombocytopenia occurred. Toxicities were recorded and graded according to the NCI CTC version 2.0 after each cycle of treatment.

Radiological imaging was repeated every 6 weeks to assess tumor response until disease progression, completion of study treatment or discharge of patient from study. Tumor responses were evaluated according to standard RECIST criteria [10]. CR was defined as disappearance of all clinical and radiological evidence of tumor. PR was considered as at least a 30% decrease in the sum of longest diameter (LD) of target lesions taking as reference the baseline sum. Progressive disease (PD) was defined as at least a 20% increase in the sum of LD of measured lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Stable disease (SD) was considered as steady state of disease in which there was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Patients who achieved a CR or PR without intolerable toxicity could continue treatment until disease progression or until 2 cycles after confirmed response. Patients with no evidence of progression or response were planned to receive a maximum of 6 cycles unless the investigator believed the patient would benefit from continued treatment.

Definitions of DLT and maximum tolerated dose (MTD)

DLT was defined as any first-cycle, non-hematological toxicity grade 3 or above (except alopecia or inadequately controlled nausea and vomiting), grade 4 neutropenia for 7 days or more, febrile neutropenia, grade 4 thrombocytopenia or thrombocytopenic bleeding, or dose delay of more than 2 weeks due to drug-related toxicity.

Successive cohorts of at least three patients were treated at each dose level until DLT, as defined above, was reached. If a patient was discontinued due to PD or intercurrent illness unrelated to toxicity before reaching the end of cycle 1, an additional patient could be enrolled at the same dose level to ensure a minimum of three evaluable patients. If none of the three patients experienced DLT, then dose escalation could occur to the next higher dose level. If any of the three patients

experienced DLT at a dose level, three additional patients were enrolled to that same dose level. Dose escalation to the next higher dose level may continue so long as none of the first three patients, or up to one of six patients in an expanded cohort, encountered DLT. If two or more patients at any dose level experienced DLT, then that dose level was considered to have exceeded the MTD and the dose level immediately preceding that was designated as the RPTD. The cohort treated at the RPTD was expanded to six patients to further assess safety and side-effects. Intrapatient dose escalation was not allowed.

Table 1 Patient characteristics

Median age [years (range)]	55 (43–67)
Gender (M:F)	10:9
Performance status (0:1:2)	9:8:2
Malignancy	
nasopharyngeal cancer	6
endometrial cancer	3
unknown primary	3
ovarian cancer	2
malignant mixed Mullerian tumor	1
colorectal cancer	1
neuroendocrine	1
sino-nasal	1
leiomyosarcoma	1
No. prior regimens (0:1:2:3:4:5:6)	9:0:4:2:3:0:1
Prior therapy	
chemotherapy and radiation	4
chemotherapy only	6
radiation only	7
none	2
Target/non-target sites	
median (range)	3 (0–9)/2 (0–6)
liver	7/3
lung	3/3
nodes	7/5
abdomen	1/1
pelvis	5/5
ascites	0/3
other	6/4
Median cycles/patient (range)	4 (1, 8)
Total cycles	76
Best response	
CR	0
PR	6
SD	5[a]
PD	8

[a]One patient had an unconfirmed PR, therefore considered as SD.

Treatment plan

The study was initially designed to administer G at 800 mg/m^2 on days 1 and 8, and A at 40 mg/m^2 plus P at 50 mg/m^2 on day 2, every 3 weeks, as the starting dose level. Examination of the safety data from the three patients treated at this starting dose level revealed an unacceptably high frequency of DLT, in the form of myelosuppression. As a result, the study was amended, and the treatment plan was re-defined to adjust the doses and scheduling of the three agents. As weekly low-dose A has been shown to be less myelosuppressive than higher doses given 3-weekly [11], the dose of this drug was decreased to a maximum of 40 mg/m^2 per cycle split weekly on days 1 and 8. Initially, A and P were given on day 2 supported by data that suggested improved activity of P when given after G [12]. As this schedule was no longer practical or convenient due to the need to split A into weekly doses, the protocol was revised to administer all three drugs on day 1, and G and A only on day 8. The modified start doses were: G 800 mg/m^2 infused i.v. over 30 min on days 1 and 8, A 15 mg/m^2 given as an i.v. bolus on days 1 and 8, and P 50 mg/m^2 infused i.v. over 60 min on day 1. In addition, a combination of G and A without P was developed for those patients who were not deemed as appropriate candidates to receive this drug. Treatment cycles were repeated every 3 weeks. All patients receiving P had adequate hydration and pre-medication with a 5-HT_3 antagonists and dexamethasone as per protocol. Pre-medication for the treatment days without P could include the above or other anti-emetic regimens at the discretion of the treating physician. Details of the dose escalation steps, which actually took place in this trial, are listed in Table 2 below.

Dose modifications

Patients were required to have ANC $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and all non-hematological toxicity (excluding alopecia) resolved to grade 1 or better before initiation of each cycle. After cycle 1, dose reductions and delays were permitted as deemed necessary for patient safety. Occurrence of any toxicity meeting the criteria for DLT as defined above prompted a dose reduction of one dose level for later cycles. Reduced

Table 2 DLT and actual dose escalations

Dose level	Dose (mg/m^2)	No. of patients with DLT/no. of patients at dose level	Description of DLT
GAP1	G 800 (days 1 and 8); A 40 (day 2); P 50 (day 2)	2/3	1=grade 4 thrombocytopenia, febrile neutropenia; 2=grade 4 thrombocytopenia, grade 3 diarrhea, grade 3 dehydration, grade 3 hypokalemia
GAP2	G 800 (days 1 and 8); A 15 (days 1 and 8); P 50 (day 1)	0/3	
GAP3	G 800 (days 1 and 8); A 20 (days 1 and 8); P 50 (day 1)	0/3	
GAP4	G 1000 (days 1 and 8); A 20 (days 1 and 8); P 50 (day 1)	2/3	1=febrile neutropenia; 2=grade 3 fatigue
GAP3a	G 800 (days 1 and 8); A 20 (days 1 and 8); P 50 (day 1)	2/2	1=febrile neutropenia; 2=febrile neutropenia
GAP2a	G 800 (days 1 and 8); A 15 (day 1 and 8); P 50 (day 1)	1/3	1=febrile neutropenia
GA1	G 1000 (days 1 and 8); A 50 (day 1)	1/1	1=febrile neutropenia
GA2	G 1000 (days 1 and 8); A 20 (days 1 and 8)	0/1	

doses were not re-escalated. Patients who required more than two dose reductions were removed from the study for unacceptable toxicity. In the event of toxicity at the first or second dose level, treating physicians may elect to reduce dose of the responsible drug(s) by a further 20%. G on day 8 was reduced to 75% if ANC $0.5–1.0 \times 10^9$/l or platelets $50–100 \times 10^9$/l and held if ANC $< 0.5 \times 10^9$/l or platelets $< 50 \times 10^9$/l. A was omitted on day 8 if was $< 1.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l. The use of hematopoietic growth factors was permitted only in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator, but must not be substituted for a required dose reduction.

Statistical analyses

Summary statistics were used to describe the patient population. The Kaplan–Meier method was used to estimate overall and progression-free survival (PFS) statistics. Dose intensity, as shown in Table 3, was calculated for each patient and for each drug by dividing the cumulative dose received by the expected dose, where the expected dose was the number of planned treatments per cycle multiplied by the adjusted number of cycles multiplied by the initial dose received of drug (in mg). The adjusted number of cycles is the number of days divided by 21, which accounts for patients with treatment delays. Thus, for instance, a patient who completes 2 cycles of treatment in 42 days with no reductions or missed doses had 100% dose intensity, but a patient who completes 2 cycles in 49 days had 86% dose intensity.

Results

Patient characteristics

Nineteen patients were accrued to this study from November 2001 to May 2004. All patients were eligible and evaluable for objective response. Patient characteristics are summarized in Table 1. The median age was 55 (range 43–67). In total, nine men and 10 female were enrolled in the study. There was a median of three target lesions per patient, with a maximum of nine target lesions for one patient. Of the patients, 89% had ECOG performance status 0 or 1. Primary tumors were from a variety of different sites, with nasopharyngeal (32%), unknown primary (16%) and endometrial (16%) carcinomas being the most common locations. Ten patients had previous chemotherapy regimens (four patients had two prior chemotherapy regimens, two patients had three prior chemotherapy regimens, three patients had four prior chemotherapy regimens and one patient had six prior chemotherapy regimens). Seven patients had received prior radiation without chemotherapy and four patients had both therapeutic modalities. Nine patients were chemonaive.

Dose escalation

A total of 76 cycles of treatment were given and the median number of cycles administered per patient was 4 (range of 1–8). The actual study dose escalation scheme is shown in Table 2, and the total number of patients and cycles delivered at each dose level is shown in Table 3.

The first three patients were treated at the initial dose level of G 800 mg/m^2 (days 1 and 8), A 40 mg/m^2 (day 2) and P 50 mg/m^2 (day 2) [GAP1]. Two of the three patients enrolled at this dose level developed DLT. One patient developed grade 4 thrombocytopenia and febrile neutropenia, whereas the other experienced grade 4 thrombocytopenia and grade 3 diarrhea together with grade 3 dehydration and hypokalemia. Due to this high frequency of DLT mostly in the form of myelosuppression in the first dose level, the study was amended and the treatment plan was re-defined to adjust the doses and scheduling of the three agents. The next level after adjusting the doses consisted of G 800 mg/m^2 and A 15 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1) [GAP2]. Three patients were treated at this dose level and all of them tolerated the treatment well without DLT. The next dose level [GAP3] intended to escalate the A dose, and consisted of G 800 mg/m^2 and A 20 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1). None of the three patients enrolled at this dose level encountered any DLT. Three patients were then treated at the next dose level [GAP4], which intended to escalate the G dose, and consisted of G 1000 mg/m^2 and A 20 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1). One patient developed febrile neutropenia and one grade 3 fatigue. The patient who developed febrile neutropenia presented simultaneously grade 3 elevations of AST and ALT that were attributed to a concomitant episode of cholangitis rather than treatment toxicity. Considering that DLT occurred in two of three patients at dose level GAP4, this level was therefore considered to have

Table 3 Number of patients, treatment cycles and mean dose intensity of drugs at each dose level

Dose level	Dose (mg/m^2)	No. of patients	No. of cycles	G mean dose intensity (%)	A mean dose intensity (%)	P mean dose intensity (%)
GAP1	G 800 (days 1 and 8); A 40 (day 2); P 50 (day 2)	3	14	75.9	84.7	82.6
GAP2	G 800 (days 1 and 8); A 15 (days 1 and 8); P 50 (day 1)	6	26	97.5	91.5	99.6
GAP3	G 800 (days 1 and 8); A 20 (days 1 and 8); P 50 (day 1)	5	15	77.6	77.5	76.0
GAP4	G 1000 (day 1 and 8); A 20 (days 1 and 8); P 50 (day 1)	3	13	74.7	77.8	99.4
GA1	G 1000 (days 1 and 8); P 50 (day 1)	1	2	87.0	99.3	–
GA2	G 1000 (days 1 and 8); P 20 (day 1 and 8)	1	6	96.6	97.1	–
Total		19	76			

exceeded the MTD and additional patients were enrolled at the preceding dose level [GAP3a, same doses as GAP3]. Two episodes of DLT however, (both febrile neutropenia) were observed in the first two patients enrolled in the expanded GAP3a dose level, leading to further dose de-escalation to level GAP2a [same doses as GAP2]. One of these two patients presented a grade 3 elevation of ALT that was related to progressive disease. At the expanded dose level GAP2a, one DLT of febrile neutropenia was observed out of three additional patients. As a result, a total of one of six patients treated at the dose levels GAP2 and GAP2a encountered DLT. This dose level, which consisted of G 800 mg/m^2 and A 15 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1), was declared as the RPTD.

For the cohorts of patients who received treatment without P, the first dose level consisted of G 1000 mg/m^2 (days 1 and 8) and A 50 mg/m^2 (day 1) [GA1]. One patient treated at this dose level developed febrile neutropenia as DLT. After the protocol amendment to split the A dose, one patient was treated at a new dose level that consisted of G 1000 mg/m^2 and A 20 mg/m^2 (both days 1 and 8) [GA2] without DLT observed.

Table 4 Dose reductions, delays and missed doses

Dose Level	Dose reductions (patients/cycles)	Dose delays (patients/cycles)	Missed doses (patients/cycles)
GAP1	1/4	2/3	2/3 – G[a]
GAP2	0/0	2/3	1/1 – A[b]
GAP3	1/1	3/3	0/0
GAP4	0/0	2/5	2/2 – A, 1/1 – G
GA1	1/1	0/0	0/0
GA2	0/0	0/0	0/0

[a]G: missed G doses only.
[b]A: missed A doses only.

Dose intensity, reductions, delays and omissions

The mean dose intensities of each study drug actually delivered at each dose level are listed in Table 4. For the four dose levels which evaluated all three study drugs [GAP1, GAP2, GAP3 and GAP4], the overall average dose intensities for all three drugs were 81.1, 96.2, 77.0 and 84.0%, respectively. At the RPTD of G 800 mg/m^2 and A 15 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1), the mean dose intensities of all three drugs were the highest among all four GAP dose levels.

The number of episodes of dose reductions, delays and missed doses for each drug are shown in Table 3. In total, out of 76 treatment cycles there were six episodes (8%) of dose reductions and 14 episodes (18%) of treatment delays. Two patients for 3 cycles missed their dose of G at dose level GAP1; one patient for 1 cycle missed their dose of A at dose level GAP2. At dose level GAP4, there were two patients who each missed one dose of A and one patient for 1 cycle received only one dose of G.

Toxicity

Selected toxicities are summarized in Tables 5 and 6. The most frequent adverse events were anemia (18 (95%) patients in 75 (99%) cycles), lymphopenia (18 (95%) patients in 73 (96%) cycles), neutropenia (18 (95%) patients in 71 (93%) cycles) and fatigue (18 (95%) patients in 66 (87%) cycles).

Hematological toxicity

The most frequent grade 3/4 toxicities were hematological including neutropenia in 13 patients [in 38 (50%) of all treatment cycles], leukopenia in 13 patients (in 36 (47%) of all treatment cycles), lymphopenia in 10 patients (in 27 (36%) of all treatment cycles) and

Table 5 Hematological adverse events (all grades)

Dose level	Total no. of patients/ cycles	All grades adverse events (patients/cycles)				
		Anemia	Leukopenia	Neutropenia	Lymphopenia	Thrombocytopenia
GAP1	3/14	3/14	3/14	3/14	3/12	3/12
GAP2	6/26	6/26	5/23	6/24	6/26	5/16
GAP3	5/15	5/15	5/15	5/14	5/15	5/12
GAP4	3/13	2/12	2/12	2/12	2/12	2/8
GA1	1/2	1/2	1/2	1/2	1/2	0/0
GA2	1/6	1/6	1/6	1/5	1/6	1/6

Table 6 Non-hematological adverse events (all grades)

Dose Level	Total no. of patients/cycles	All grades adverse events (patients/cycles)						
		Abdominal pain or cramping	Diarrhoea	Fatigue	Nausea	Vomiting	Stomatitis	Sensory neuropathy
GAP1	3/14	1/6	1/2	3/14	3/6	2/2	1/2	1/6
GAP2	6/26	4/14	3/3	5/21	3/10	1/2	1/3	3/18
GAP3	5/15	2/3	0/0	5/10	2/7	2/3	0/0	0/0
GAP4	3/13	2/7	0/0	3/13	2/8	1/1	2/2	0/0
GA1	1/2	0/0	0/0	1/2	0/0	0/0	0/0	0/0
GA2	1/6	0/0	0/0	1/6	1/1	1/2	0/0	0/0

thrombocytopenia in eight patients (in 16 (21%) of all treatment cycles). Seven patients required packed red blood cell transfusions and three patients required platelet transfusions. Four patients each had one episode of neutropenic fever during their entire duration of study therapy and all these episodes resolved with parenteral antibiotics treatment. All febrile neutropenic episodes occurred during cycle 1 except for one patient in cycle 3.

Non-hematological and biochemical toxicity

No grade 4 non-hematological toxicities were observed in this study. Grade 3 abdominal pain/cramping occurred in four patients (in 8 (11%) of the cycles). Other grade 3 non-hematological toxicities included fatigue, diarrhea and headache. These events were however, infrequent, occurring in less than 5% of treatment courses. Grade 3/4 electrolyte disturbances were infrequent. There were no cases of treatment-related death.

Response and survival

Although efficacy was not the primary endpoint of this study, promising anti-tumor activity was observed. In all, 19 patients were evaluable for tumor response. Six patients achieved an objective PR, resulting in a response rate of 31.6% (95% confidence interval 12.6–56.6%) by intention-to-treat analysis. Of these six patients, three have since progressed. Six patients had SD, including one patient who had an unconfirmed PR at cycle 2 and symptomatic progression in cycle 4, and was removed from study. The median PFS was 5.3 (range 1.6–NA) months. Four patients died at 0.7, 1.5, 3.1 and 7.2 months after starting GAP treatment. The remaining 15 patients were alive as of last follow-up. The median survival duration for all study patients was 10.6 (range 2.5–34.3) months.

Discussion

The current phase I study was conducted to assess the feasibility of the GAP combination, determine the RPTD and describe the toxicity profile of the combination. This regimen was conceived based on different mechanisms of anti-tumor activity of these agents, synergistic effects, and broad efficacy of the combination of P and G in different tumor types [6–9]. Non-overlapping toxicity profiles of these agents further support such a combination.

The DLT in this study was neutropenic fever. Grade 3/4 neutropenia represented the most frequent severe hematological adverse event observed, with an incidence of 68% among all study patients in 50% of all treatment cycles. Even with this high frequency of neutropenia the rate of neutropenic fever was low at 5% of cycles (21% of patients). Grade 3/4 thrombocytopenia and anemia were seen in 42 and 26% of the patients, respectively. These toxicities were expected and consistent with rates reported in previous studies combining these drugs. Von der Maase *et al.* observed frequencies of grade 3/4 neutropenia, thrombocytopenia and anemia in 71, 56 and 27% of patients in a multicenter study assessing the combination of G and P versus the MVAC regimen in advanced transitional cell carcinomas of the bladder [8]. Yang *et al.* who combined A and G in patients with advanced hepatocellular carcinoma reported respective frequencies of 51, 26 and 46% of grade 3/4 neutropenia, thrombocytopenia and anemia, as well as a 12% rate of febrile neutropenia, among 35 patients treated in the phase II part of their trial [3]. Similarly, Thigpen *et al.* observed grade 3/4 leukopenia of 62% (rate of neutropenia not provided) among 278 patients when combining P and A for the treatment of advanced endometrial carcinoma [4].

Mild to moderate fatigue represents the most common non-hematological toxicity (18 (95%) patients in 66 (87%) cycles) in this study. No grade 4 non-hematological toxicities were observed. Other grade 3 toxicities encountered included fatigue, diarrhea, headache and abdominal pain or cramping. These events however, were infrequent, with abdominal pain/cramping occurring in 11% of treatment cycles and the other non-hematological toxicities occurring in less than 5% of cycles. It should be noted that no grade 3/4 nausea vomiting was seen in our study, in contrast to the results of previous regimens where A was used in combination with P [4]. This observation could be explained by the lower doses of the anthracycline used in this study and its splitting into weekly doses. Also, the tolerability of this regimen is supported by the lack of grade 3/4 stomatitis and neurotoxicity that typically would have been expected from the use of these two drugs.

The combination of GAP showed anti-tumor activity in a variety of tumor types. Of 19 patients evaluable for response, six patients (31.6%) with different tumor types (two nasopharyngeal carcinomas, two ovarian cancers, one endometrial cancer and one cancer of unknown primary) had PRs. The observed anti-tumor activity of the GAP triplet is comparable with that reported in studies evaluating doublets of these anti-neoplastic agents. Other investigators have reported objective response rates in the range of 40–50% in different tumor types using combinations of two of these three drugs, although the prior treatment status of patient populations might differ from study to study [2–4, 7–9]. The comparison of doublets versus triplets has been made in some cancers, such as non-small cell lung cancer, with disappointing outcomes for the latter due to increased toxicity and equivalent or inferior efficacy [13].

Although the objective response rate observed using the GAP triplet in our study appears similar to that expected

of doublet combinations of the study drugs, the prolonged remission durations of some of the responders were encouraging. While the therapeutic benefit using this triplet combination over doublet combinations is unproven, it is reasonable to consider this regimen in situations where visceral organ toxicities are of concern. The dosing of the GAP triplet is primarily limited by bone marrow toxicity, whereas non-hematological toxicities such as cardiotoxicity, nephrotoxicity, neurotoxicity, and gastrointestinal toxicity are relatively spared.

Conclusion

GAP is an active and tolerable treatment combination, with minimal visceral organ toxicities. The DLT in this phase I study was neutropenic fever; the recommended doses for further phase II trials are G 800 mg/m^2 and A 15 mg/m^2 (both on days 1 and 8), and P 50 mg/m^2 (day 1), repeated every 3 weeks.

References

1 Dodd PM, McCaffrey JA, Hilton S, Mazumdar M, Herr H, Kelly WK, *et al.* Phase I evaluation of sequential doxorubicin, gemcitabine then ifosfamide paclitaxel cisplatin for patients with unresectable or metastatic transitional-cell carcinoma of the urothelial tract. *J Clin Oncol* 2000; **18**:840–846.

2 Nanus DM, Garino A, Milowsky MI, Larkin M, Dutcher JP. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. *Cancer* 2004; **101**:1545–1551.

3 Yang TS, Wang CH, Hsieh RK, Chen JS, Fung MC. Gemcitabine and Doxorubicin for the treatment of patients with advanced hepatocellular carcinoma: a phase I–II trial. *Ann Oncol* 2002; **13**:1771–1778.

4 Thigpen JT, Brady MF, Homeslesy HD, Malfetano J, DuBeshter B, Burger RA, *et al.* Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 2004; **22**:3902–3908.

5 Kalofonos HP, Bafaloukos D, Kourelis TG, Malfetano J, DuBeshter B, Burger RA, *et al.* Adriamycin and *cis*-platinum as first-line treatment in unresectable locally advanced or metastatic adult soft-tissue sarcomas. *Am J Clin Oncol* 2004; **27**:307–311.

6 Crino L, Scagliotti G, Marangolo M, Figoli F, Clerici M, De Marinis F, *et al.* Cisplatin–gemcitabine combination in advanced non-small-cell lung cancer: a phase II study. *J Clin Oncol* 1997; **15**:297–303.

7 Cardenal F, López-Cabrerizo MP, Antón A, Alberola V, Massuti B, Carrato A, *et al.* Randomized phase III study of gemcitabine–cisplatin versus etoposide–cisplatin the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 1999; **17**:12–18.

8 Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; **18**:3068–3077.

9 Crump M, Baetz T, Couban S, Belch A, Marcellus D, Howson-Jan K, *et al.* Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *Cancer* 2004; **101**:1835–1842.

10 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.

11 Gundersen S, Kvinnsland S, Klepp O Lund E, Hannisdal E, Host H. Chemotherapy with or without high-dose medroxyprogesterone acetate in oestrogen-receptor-negative advanced breast cancer. Norwegian Breast Cancer Group. *Eur J Cancer* 1992; **28**:390–394.

12 Shepherd FA, Abratt R, Crino L, Green M, Sandler A, Steward W, *et al.* The influence of gemcitabine and cisplatin schedule on response and survival in advanced non-small cell lung cancer. *Lung Cancer* 2000; **30**:117–125.

13 Bunn Jr PA. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? *J Clin Oncol* 2002; **20** (**18 Suppl**):23S–33S.