demonstrated [2]. DAC has also shown antineoplastic activity both *in vitro* and against the murine leukaemias AKR, P388 and L1210. The need for prolonged exposure (S-phase specificity) and chemical instability has led to an unusual administration schedule, investigated in both phase I and II studies [3, 4]. We report our findings with this schedule of DAC in patients with cervical cancer who failed on conventional chemotherapy regimens.

Patients were eligible for this study if they had progressive (recurrent and/or metastatic) cervical cancer, not amenable to local therapies. Other criteria included: age less than or equal to 75 years, WHO performance status 2 or under, life expectancy greater than 2 months, measurable/evaluable disease outside irradiated areas, therapy-free interval greater than or equal to 4 weeks (for previous mitomycin or nitrosoureas $\geq$ 6 weeks), resolved toxicities, adequate bone marrow (white blood cells $\geq 4 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l), liver and renal function and informed consent. DAC (diluted in 250 ml 0.9% normal saline) was given at a dose of 75 mg/m^2 as an intravenous infusion over 1 h, three times on day 1 over 7 h intervals, repeated every 5 weeks. DAC was postponed by 1 week if there was no full haematological recovery. Dose adjustments were based on nadir counts and treatment delay due to myelosuppression in the previous course. WHO criteria for toxicity and response (including early progression) were used, but "no change" was defined as 12 weeks' disease stabilisation. Early death due to malignant disease was regarded as treatment failure.

17 patients entered the study. 2 were not eligible (all lesions in irradiated areas). The remaining patients had a median age of 50 years (30–75), a median performance status 2 (0–2), and previous treatment with chemotherapy (14 had been treated with cisplatin-containing regimens). 13 had also received radiotherapy. Histology was: squamous 13, adenosquamous 1 and adenocarcinoma 1. All patients had distant metastases, but 7 also had local disease (5/7 recurrent). 1 patient, with unchanged lesions after 7 weeks, died after 11 weeks of unknown cause, leaving 14 patients fully evaluable. None of the patients responded to DAC, or showed even disease stabilisation. 3 patients progressed after the first cycle, and 3 died early due to malignant disease. 1 patient died due to toxicity (grade 4 myelosuppression, septic shock) after the second cycle. This patient also had grade 1 nephrotoxicity after the first cycle. Overall lowest white blood cell counts (median 2.0×10^9/l, range $0.1–3.7 \times 10^9$/l) were recorded on day 21, and platelet counts (median 139×10^9/l: range $19–344 \times 10^9$/l) on day 14. The most frequent non-haematological toxicities were nausea and/or vomiting (40%) usually of mild intensity, and 1 patient had diarrhoea.

Our results indicate that DAC has less than a 5% chance of greater than 20% activity in patients with cervical cancer, previously treated with chemotherapy. It is therefore considered inactive in these circumstances. Toxicities observed are in agreement with earlier data [4]. Moreover, we observed drug-related reversible renal toxicity in 1 patient, which had been described in a phase I study using the same administration schedule [3].

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A Phase I Study of Cisplatin, 5-fluorouracil and Leucovorin with Escalating Doses of Hydroxyurea in Chemotherapy Naive Patients

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SUCCESSFUL MODULATION of 5-fluorouracil (5-FU) by leucovorin has been described in experimental models [1, 2] and patients with colorectal cancer [3, 4]. At the University of Chicago, we have attempted to increase the efficacy of cisplatin and 5-FU in head and neck cancer by modulation of 5-FU with high dose oral leucovorin (PFL) [5, 6]. These trials have led to the definition of recommended doses and showed a high activity for the combination. Hydroxyurea is an S-phase specific ribonucleotide reductase inhibitor which has synergistic cytotoxicity with 5-FU [7]. This may be due to depletion of cellular deoxyuridine monophosphate (dUMP) pools by hydroxyurea, allowing the 5-FU metabolite 5-FdUMP to bind more effectively to its target enzyme, thymidylate synthase. The combination of hydroxyurea and leucovorin, therefore, might optimally modulate 5-FU by increasing the binding of 5-FdUMP to thymidylate synthase, as well as increasing ternary complex formation and stability. In this phase I study, we added hydroxyurea to the PFL combination to define the optimal doses for both 5-FU and hydroxy-

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urea, and their dose-limiting toxicities. Since we anticipated the future neoadjuvant use of this combination, we studied exclusively patients who had not received chemotherapy.

The study began in March 1989 and ended in February 1990. Eligibility criteria included histological or cytological documentation of neoplastic disease for which no standard therapy existed, a performance status of 0–2, normal end-organ function and informed consent. Cisplatin (100 mg/m^2) was administered over 2 h; at 6 h, a 5-day continuous infusion of 5-FU was started at 600 mg/m^2 per day. Oral leucovorin (100 mg) was administered every 4 h from start of treatment to completion of the 5-FU infusion (total of 32 doses). Hydroxyurea was also administered from the beginning, every 12 h for a total of 10 doses. Dose levels of hydroxyurea were 500 mg, 1000 mg alternating with 500 mg, or 1000 mg, all twice daily. Cycles were repeated every 21 days and a minimum of 3 patients were treated at a given dose level. If grade 3 toxicity was observed in 1 patient, up to 6 patients were treated. Dose escalation continued until more than 50% of patients at a dose level (a maximum of 3 patients) developed grade 3 toxicity, or more than 1 patient developed grade 4 toxicity. Doses were not escalated in individual patients, and standard response criteria were used.

18 patients were entered on this protocol (9 men, 9 women). The median age was 64 years (40–79), and performance status was 0 (1 patient), 1 (12 patients) and 2 (5 patients). 9 patients had non-small cell lung cancer (NSCLC), 3 had colorectal cancer, 3 had metastatic disease of unknown primary, and 1 each had cancer of the head and neck, pancreas and cervix uteri. 15 patients were evaluated for toxicity (Table 1). During levels 1–3, the dose of hydroxyurea was increased from 1000 mg to 2000 mg daily. This resulted in grade 3 myelosuppression in 2 of 3 patients treated with 2000 mg hydroxyurea. Therefore, a hydroxyurea dose of 1500 mg daily, administered as 1000 mg alternating with 500 mg every 12 h, was considered the maximally tolerated dose in this combination. This dose of hydroxyurea also produced acceptable non-haematological toxicity. To determine whether escalation of 5-FU to 800 mg/m^2 per day was feasible, we treated 3 additional patients with 800 mg/m^2 per day of 5-FU and the recommended hydroxyurea dose of 1500 mg daily on level 4. Grade 4 myelosuppression was observed in 2 of 3 patients and all 3 patients developed grade 3 mucositis, indicating excessive toxicity at this dose level.

16 patients were evaluated for response. 2 had a partial response, 1 a minor response, 1 patient with only evaluable disease had objective disease regression and 7 patients had stable disease. Of 8 evaluable patients with NSCLC, 2 responded and 3 had stable disease. Of 3 patients with colorectal cancer, 1 had a minor response and 2 had stable disease. The fourth responding patient had adenocarcinoma of unknown primary site.

Based on these data we recommend a dose of 600 mg/m^2 per day of 5-FU and 1500 mg daily of hydroxyurea. Compared to the original PFL regimen [5, 6] a 25% decrease in the 5-FU dose is necessary to allow for the addition of hydroxyurea. This might offset any therapeutic advantage from hydroxyurea, although phase II trials are needed to define the activity of PFL-hydroxyurea. Given the activity of the original PFL combination in head and neck cancer [5, 6] and NSCLC [8], these disease sites might be well suited for further investigating this combination, as well as gastrointestinal malignancies in which the modulation of 5-FU by leucovorin has already been described.

Table 1. Toxicities (cycle 1)

5-FU/HU dose (mg/m^2)	No. of patients	Grade 0	1	2	3	4
		White blood cell nadir				
600/1000	6	1	4	0	1	0
600/1500	3	1	1	1	0	0
600/2000	3	0	0	1	1	1
800/1500	3	0	0	1	0	2
		Platelet nadir				
600/1000	6	5	0	0	1	0
600/1500	3	3	0	0	0	0
600/2000	3	2	0	0	1	0
800/1500	3	1	0	0	1	1*
		Mucositis/other toxicities				
600/1000	6	2	0	4	0†	0
600/1500	3	0	2	1	0‡	0
600/2000	3	0	1	1	1§	0
800/1500	3	0	0	0	3	0

HU = hydroxyurea.
*Neutropenic fever (1), †Grade 3 proctitis (1) and grade 3 nausea/vomiting (1 other), ‡grade 3 nausea/vomiting (1), §grade 3 renal (1).

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