these patients. The data on the efficacy of dacarbazine in head and neck cancer are limited, with no remissions observed in 33 patients treated in phase I–II studies [1–3]. Patients received 250–350 mg/m^2 by intravenous push for 5–10 consecutive days every 3–5 weeks. If calcium ions are supplied to preclude hypotensive episodes dacarbazine can be given up to a dose of 1.9 g/m^2 every 3 weeks [4]. From this experience a dose of 1.2 g/m^2 was selected for study in SCCHN.

All patients had histologically confirmed squamous cell carcinoma of the head and neck. Eligibility criteria included: locoregionally recurrent or metastatic disease not amenable to curative therapy, Karnofsky index 60% or more, measurable or evaluable disease, leucocytes over 3500/μl, platelets over 100 000/μl, serum creatinine 1.2 mg/dl or less and bilirubin 2 mg/dl or less. Patients signed an informed consent form.

Every 3 weeks patients received dacarbazine 1.2 g/m^2 as an intravenous infusion over 20 min, with 5 ml 10% calcium gluconate at the start and 10 and 20 min from the beginning of therapy. Additional calcium gluconate was given if the systolic blood pressure was lower than 80 mm Hg or heart rate higher than 140/min within 90 min from the infusion. Special care was taken to protect dacarbazine from light: the drug was quickly reconstituted, and the flask and tubing were wrapped with tinfoil. Weekly blood cell counts were done in the first 2 cycles; if the haematological nadir was grade 1 or lower after the first course, the dacarbazine dose was increased by 20%. In the absence of progression, patients received at least 2 cycles. WHO criteria for response to therapy and toxicity were used [5].

24 patients entered the study. 2 were evaluable only for toxicity (early death in 1 case, cessation of treatment due to cardiac toxicity in the second) and 1 patient was lost to follow-up. The characteristics of the evaluable patients are shown in Table 1. Response to therapy was as follows: partial remission 1, stable disease 2 and progressive disease 18 (9 after only 1 cycle). The overall response rate was 5% (95% CI, 0–9%). The partial remission occurred in a patient progressing on cisplatin-based therapy and lasted 8 weeks.

23 patients evaluable for toxicity received 45 courses of dacarbazine (median 2, range 1–5), 11 had only 1 cycle and the dose was increased in 7 without a significant increase in toxicity.

Table 1. Characteristics of 21 evaluable patients

M/F	21/0
Mean Karnofsky index (range)	70 (60–100)
Mean age (yr) (range)	57 (36–74)
Primary site	
Larynx	8
Oropharynx	6
Oral cavity	6
Hypopharynx	1
Sites of disease	
Primary tumour	1
Primary and metastatic	5
Metastatic only	15
Measurable disease	17
Evaluable disease	4
Previous therapy	
Surgery	13
Radiotherapy	16
Chemotherapy	13

3 patients had less than 3000 leucocytes/μl and 1 less than 100 000 platelets/μl. Nausea and vomiting grade 2 or higher occurred in 16 patients, diarrhoea grade 1 in 9, moderate pain during dacarbazine injection in 11, a systolic blood pressure lower than 80 mm Hg in 7 and a heart rate higher than 140/min in 2. A patient with ectopic atrial beats had prolonged hypotension that led to interruption of dacarbazine therapy.

Our results indicate that dacarbazine in high intermittent doses has no activity in patients with advanced squamous cell carcinoma of the head and neck.

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5-aza-2′-deoxycytidine in Advanced or Recurrent Cancer of the Uterine Cervix

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5-aza-2′-deoxycytidine (DAC) acts by incorporation into DNA, after conversion to the nucleotide by deoxycytidine kinase [1]. This leads to hypomethylation of DNA, which has been associated with activation of gene expression and induction of cell differentiation. A direct cytotoxic and growth inhibitory effect on leukaemic cells resistant to differentiation has been

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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

Everett E. Vokes, Mark J. Ratain, Linda Janisch, Philip C. Hoffman, Harvey M. Golomb and Richard L. Schilsky

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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