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An Experimentally Designed High Dose Simultaneous Combination of a Diaminopyrimidine and Folinic Acid for the Treatment of Human Malignancies

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Abstract—*Eighty patients with previously treated advanced malignant disease were treated with 2,4-diamino-5-(3',4'-dichlorophenyl)-6-methyl pyrimidine (DDMP) and folinic acid. Both compounds were given together every 7 days. The dose of DDMP ranged from 1 to 10 mg/kg. The average weekly dose of folinic acid was 2.1 mg/kg. Of 75 assessable patients, 14 responded with a 50% reduction in tumour size, 7 showed partial regressions with a 20–50% reduction, 6 showed disease arrest and 48 failed to respond. No responses were seen from DDMP doses less than 3 mg/kg/wk administered for less than 3 weeks. Toxicity to bone marrow and other tissues was far less than in other published studies using different scheduling of these two compounds. The safety of this protocol, together with the encouraging preliminary results justify further trials especially for tumours in sites in which DDMP reaches high concentrations, e.g., kidney, brain, skin and pancreas, where current drug treatment is relatively ineffective.*

INTRODUCTION

DDMP possesses antitumour acitivity in tissue culture, animals and man[1–8]. Its toxicity to normal tissues led to its rejection as an antitumour drug in man nearly 30 yr ago. Folinic acid is known to reduce this toxicity by varying extents, depending on the dose and scheduling employed[7–10].

In 1973, experimental results suggested that better antitumour effects might be obtained if DDMP was given in the highest possible dose over the longest possible time [1]. In addition, the concurrent administration of folinic acid with DDMP was shown selectively to protect methotrexate (MTX)-sensitive cells without loss of cytotoxic effect against MTX-resistant tumour cells [10–12]. Preliminary clinical studies based on these findings showed that the simultaneous combination of DDMP and folinic acid could be given perfectly safely and with definite antitumour effect provided certain precautions were rigorously observed [8, 13]. This report confirms these results in a larger number of patients using higher doses of DDMP than was previously thought possible or safe.

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MATERIALS AND METHODS

Seventy-nine of the patients were treated at the Royal Marsden Hospital, London, U.K. and 1 at St. Michael's Hospital, Toronto. Seventy five patients were assessable for response. Reasons for non-assessability were: defaulted from trial—2, and inadequate dose (i.e., less than three doses of at least 2 mg/kg/wk)—3. Criteria for entry to the trial were (a) all patients were considered by the referring clinicians to have untreatable disease, (b) all patients must have had measurable disease either on palpation or by radiological, radio-isotope scanning or ultrasonographic techniques, (c) all patients entered must have objective evidence of progressive disease.

Baseline measurements of tumour sizes were recorded before the first treatment and at regular intervals subsequently. DDMP and folinic acid (as calcium leucovorin, Lederle) were nearly always given in the out-patient department every 7 days. Both compounds were given at the same time (i.e., over 5 min). A staff nurse supervised their administration to make sure that the agents were given. On the rare occasions when patients vomited within 30 min

of therapy, this was counted as zero dose. Six patients were prone to vomiting (three before they came into the Clinic) and these were premedicated with maxolon, 10 mg intramuscularly, 45 min before therapy. Both compounds were usually given in tablet form. For patients who objected to taking large numbers of tablets, the intravenous preparation of folinic acid was given either as an injection or as a drink in orange squash. DDMP tablets, although insoluble in water, could be crushed and stirred into a suspension and could also be given as a drink.

In general the dose of folinic acid necessary for adequate protection of normal tissues was approximately two-thirds that of DDMP (i.e., a patient receiving 90 mg DDMP would be given 60 mg of folinic acid). Originally we were informed that doses of DDMP greater than 1.5 mg/kg could not be given without severe toxicity. When it became obvious that this supposition was invalid, the weekly dose of DDMP was gradually escalated (usually by giving one extra 25 mg tablet every 7 days) to doses of 3 mg/kg and beyond. The dose of simultaneous folinic acid was *always* increased proportionately. In the few patients whose platelet count fell more than 50%, equal doses of folinic acid and DDMP were given occasionally.

All patients had regular assessments of cardiac, hepatic, renal and bone marrow functions. A routine peripheral blood count (haemoglobin, total white count and absolute platelet count) was taken just before treatment each week. If there was moderate depression of the platelet count, i.e., less than 30% fall compared with baseline measurements, DDMP was omitted, but the usual dose of folinic acid was *always* given. If severe depression of the platelet count occurred, the principle of folinic acid "rescue" was applied, i.e., the patient was given folinic acid 15 mg six hourly until the marrow recovered. We then re-started the original dose of DDMP with a higher dose of simultaneous folinic acid so as to afford better protection against myelosuppression.

RESULTS

Fourteen patients responded as customarily defined (i.e., a 50% or more reduction in the product of two perpendicular diameters in all measurable lesions). The diagnoses and duration of response in these patients are summarised in Table 1.

Seven patients showed a response of between 20 and 50% tumour regression. These cases are summarised in Table 2. Six patients showed arrest of previously progressive disease. These results are shown in Table 3. In 48 patients no response was seen, as detailed in Table 4.

The extent of myelosuppression in relation to the number of treatment cycles given is shown in Table 5. Other side effects included a headache, which usually occurred the day after

Table 1. Cases showing greater than 50% objective tumour regression (14/75)

Diagnosis	Duration of response* (months)
S.C.C. lung	12
S.C.C. lung	3
S.C.C. lung	2.5
S.C.C. lung	2
Hypernephroma	44
Hypernephroma	3
Hypernephroma	12†
Hypernephroma	6
Carcinoma rectum	8
S.C.C. larynx	2
Astrocytoma (grade 4)	1
Melanoma	2.5
Melanoma	6
Melanoma	1

S.C.C.: squamous cell carcinoma.
*Duration of response is the time from the first dose of DDMP to the first evidence of tumour regression.
†Patient run over by truck while disease still regressing.

Table 2. Cases showing between 20–50% objective tumour regression (7.75)

Diagnosis	Duration of response (months)
S.C.C. lung	3
S.C.C. lung	2
S.C.C. lung	6
S.C.C. lung	5
S.C.C. tonsil	3
Oat cell carcinoma lung	1
Oat cell carcinoma lung	7

S.C.C.: squamous cell carconoma.

Table 3. Patients whose tumours ceased to progress on DDMP and simultaneous folinic acid (6/75)

Diagnosis	Duration of control (months)
Hypernephroma	11
Hypernephroma	11
Hypernephroma	15
Hypernephroma	36
Hypernephroma	18
Melanoma	6

Table 4. Non-responders, i.e., patients with progressive disease in spite of treatment with DDMP and simultaneous folinic acid (48/75)

Diagnosis	Number of patients
S.C.C. lung	11
Hypernephroma	10
Teratoma testis	2
Carcinoma prostate	2
Head and neck cancer	3 (2 S.C.C., 1 parotid adenocarcinoma)
Pleural mesothelioma	2
Carcinoma breast	3 (1 male)
A.M.L.	2
Carcinoma stomach	2
Carcinoma brain	3 (2 primary, 1 secondary from breast)
Carcinoma bladder	1
Carcinoma pancreas	1
Urothelial carcinoma	1
Melanoma	1
Adenocarcinoma from unknown primary	1
S.C.C. anus	1
Carcinoma rectum	1
Giant cell carcinoma lung	1

S.C.C.: squamous cell carcinoma.
A.M.L.: acute myeloid leukaemia.

Table 5. Bone marrow toxicity

Total number of treatments with DDMP and concurrent folinic acid	854
Number of times platelets fell below 50,000 per mm^3	18
Number of times platelets fell below 100,000 per mm^3	82
Number of times total white count fell below 1000 per mm^3	2
Number of times total white count fell below 2000 per mm^3	6
Average % drop in haemoglobin concentration as percent of baseline	19

DDMP was given, relieved by temporarily reducing the average weekly dose; a skin rash, usually erythematous or morbilliform, relieved by antihistamines or corticosteroids; and occasional looseness of the bowel, easily controlled by codeine phosphate. These non-myelosuppressive side effects are summarised in Table 6. None of these side effects significantly interfered with treatment, as summarised in Table 7.

DISCUSSION

This study illustrated several major problems in the search for potentially useful new anti-cancer drugs. First, an agent showing promise in experimental screening systems may be dismissed in Phase 1 clinical studies because it is not given optimally. In several studies DDMP has been given in various doses and combinations with folinic acid and has produced very severe toxicity to the bone marrow and the central nervous system [9, 14–19]. In these trials, however, the folinic acid was either given

Table 6. Toxicity (other than bone marrow) in 80 patients given high dose DDMP and simultaneous folinic acid

Central nervous system:	Headache	8
	"Haziness"	3
	"Giddiness"	4
	Paraesthesiae	1
	Mental stimulation	1
Muscle weakness		4
"Gastritis"		8
Skin rash		10
Nausea and/or vomiting		9
Loose bowels		4
Convulsions		0
Drug-induced death		0

Table 7. Details of drug treatment given to 80 patients on study

Average dose of DDMP mg/kg/wk	3 (range 1–10)
Average percentage of intended dose DDMP given	72.4%
Average dose of folinic acid mg/kg/wk	2.1

some time after DDMP, or else, when it was given at the same time, the dose was too small to protect the normal tissues. In addition, the dose of DDMP itself has usually been well below an average of 3 mg/kg/wk and we have seen no antitumour effect below this dose. Secondly, DDMP was rejected because it is a much weaker inhibitor of the alleged target enzyme dihydrofolate reductase compared with methotrexate [1]. Even so, it is effective both in tissue culture [10, 12] and clinically against MTX-resistant tumour cells. Assessments of possible antitumour effects based on enzyme inhibition studies alone may therefore be misleading.

The long half-life of DDMP [20] is an advantage clinically since the antitumour effect depends not only on the dose but also on a prolonged exposure. Why a substance with an apparently short half-life such as folinic acid can protect normal tissues against an agent with such a long half-life is pharmacologically puzzling, and the explanation is not yet known. It is, however, an undisputed clinical fact and has been confirmed by granulocyte colony-forming assays on the bone marrow of a patient receiving the drug [21].

The available experimental and clinical data has recently been reviewed [22]. This study confirms our previous findings [8, 13], that high dose DDMP and concurrent folinic acid is an extremely safe combination with predictable and avoidable toxicity which shows encouraging initial results in certain tumours largely resistant to current drug treatment. We earlier suggested [13] the potential value of this combination in brain tumours, where the lipophylic DDMP is likely to reach high drug concentrations. A recent preliminary study in gliomas indicates only modest activity at the low drug doses used, but recommends further evaluation at higher dosage [23]. Further studies using this protocol are indicated in these advanced cancers, and possibly in early combination with surgery and/or radiotherapy in prospective randomised trials.

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