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Phase II Clinical Trial of DDMP (2,4-Diamino-5-(3′,4′-Dichlorophenyl)-6-Methylpyrimidine) and Folinic Acid (CF) in Solid Tumors

Robert de Jager[1]*, Antonio Brugarolas[2], and Mogens Hansen[3]
(EORTC Early Clinical Trials Group)

[1] Institut Jules Bordet, 1 Rue Héger-Bordet, B-1000 Bruxelles
[2] Hospital General de Asturias, Oviedo, Spain
[3] Finseninstitute, Copenhagen, Denmark

Summary. *DDMP, a 2–4 diaminopyrimidine folate antagonist was administered PO once every 3 weeks at a fixed dose level (90 mg/m²), 24 h before a single IM injection of folinic acid (CF), to 77 patients with advanced solid tumors. CF doses were escalated in sequential sets of patients from 9–108 mg/m². Therapeutic activity was documented against epidermoid tumors of head and neck and lung only at the lower CF doses (9 and 15 mg/m²).*

Increasing CF resulted in the absence of hematologic toxicity and therapeutic activity. There was no evidence of selective bone marrow protection in this clinical study.

Introduction

DDMP is a 2–4 diaminopyrimidine inhibitor of dihydrofolate reductase (DHFR). It has a verly long half-life (180 h) and differs from methotrexate (MTX) by its lower affinity for DHFR and its lipophilic characteristics [13].

DDMP and MTX interact with DHFR in a similar manner and although the affinity for the enzyme is 1 of 100 that of MTX, it still represents tight and substantial binding to the enzyme [2, 11, 12]. DDMP does not inhibit other folate-metabolizing enzymes. Therefore the inhibition of DHFR appears to be the only mechanism of action of DDMP. Furthermore, there is no cross resistance between DDMP and MTX in a L1210 cell line resistant to MTX, because of high DHFR activity [2].

Reprint requests should be addressed to: R. de Jager
* *Present address:* I.C.I.G., Hôpital Paul-Brousse, 14–16 Avenue P.-V. Couturier, F-94800 Villejuif, France

The lipophilicity of DDMP results in two clinically exploitable advantages over DDMP:

1) *A tissue distribution* different from CF, allowing 'compartmental chemotherapy'. DDMP, unlike CF, penetrates readily into the CNS [5, 13]. The treatment of brain tumors and meningeal disease thus appears to be a possible application of this concept.

2) *Penetration of tumor cells* resistant to MTX because of a membrane transport defect common to MTX and CF. L5178Y lymphoblasts resistant to MTX because of the absence of the specific MTX/CF membrane transport mechanism are sensitive to DDMP, and the DDMP-induced cytotoxicity cannot be reversed by CF. Conversely, L5178Y lymphoblasts sensitive to MTX are also sensitive to DDMP, and DDMP cytotoxicity can be reversed by CF [6–8].

On the basis of these experiments, Hill proposed the concomitant use of DDMP and CF to allow selective protection of folate-dependent normal tissues (skin, gastrointestinal mucosa, bone marrow). Several clinical trials have demonstrated significant antitumor activity for DDMP alone and with concomitant or delayed CF administration in acute leukemias, lymphomas, and solid tumors [1, 3, 4, 9, 10, 14, 15].

The efficacy of DDMP in MTX-resistant tumors is not established, however, nor is there supporting evidence for the superiority of DDMP/CF combined treatment over DDMP alone. The question of the best dose and schedule of administration of DDMP and CF remains open.

The purpose of this study was to confirm the possibility of selectively protecting the bone marrow

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with CF while retaining the antitumor effect of DDMP. Therefore, the dose of CF was increased stepwise while DDMP was kept at a fixed dose level. The schedule and dosage of DDMP were selected from a phase I study showing that DDMP 90 mg/m^2 every 3 weeks resulted in objective tumor regression without CNS toxicity [4].

The starting dose of CF, 9 mg/m^2, was selected on the basis of previous unpublished data. CF was administered 24 h after, rather than concomitantly with DDMP, to avoid a potential negative effect of CF in MTX-sensitive tumors.

Materials and Methods

Patients with biopsy-proven, advanced solid tumors not amenable to conventional chemotherapy were eligible provided they had a performance status of 50 or above, a serum creatinine level < 1.5 mg/100 ml, and bilirubin < 2 mg/100 ml. A 4-week interval was required between prior chemotherapy and the beginning of DDMP treatment. Weekly follow-up was obtained to record performance status, tumor measurements, drug side-effects, and complete blood counts. Serum creatinine and liver function tests were obtained every 3 weeks.

DDMP was supplied by the Wellcome Research Laboratories, Beckenham, Kent, England, as 25-mg tablets. CF was purchased from commercial sources as Calcium Leukovorin in 3-mg ampules. DDMP 90 mg/m^2 PO (average dose 150 mg) was administered every 3 weeks. CF was injected IM 24 h after giving DDMP, following a dose escalation scheme in sequential sets of patients (see Table 1).

CF doses were escalated from a single dose of 9 mg/m^2 to 9 mg/m^2 every 6 h for 12 doses (total dose 108 mg/m^2). In the case of severe toxicity: skin rash, leukocyte count < 1,500/mm^3, platelet count < 50,000/mm^3, CF rescue was given as one or more doses of 9 mg/m^2 IM or IV.

An objective response was defined as a partial tumor regression with at least 50% reduction in the product of the two longest perpendicular diameters of all measurable lesions. Brain, bone metastases, and pleural effusion were not considered as criteria for evaluation.

Table 1. Therapeutic effect of DDMP 90 mg/m^2 and delayed CF administration (24 h)

CF dose (mg/m^2)	Number of patients	PR[a]	NC[b]	Progression of disease
9	19	9	7	3
15	12	2	4	6
20	10	0	3	7
30	10	0	0	10
45	10	1	0	9
108 (9 × 12)	16	1	3	12
Total	77	13 (17%)	17	47

[a] PR, partial remission
[b] NC, no change

Results

Therapeutic Response

Seventy-seven patients were treated at three different institutions. The overall response rate was 17%. At the lower CF dosages (9 and 15 mg/m^2), 11 of 31 patients showed an objective response but only 2 of 46 responded to CF doses of 20 mg/m^2 or more (see Table 1).

Responses were seen only in epidermoid tumors of head and neck and of lung. In head and neck tumors, 8 of 27 (30%) patients achieved partial remission (PR): 7 of 11 with CF 9 and 15 mg/m^2 but only 1 of 16 with higher CF doses ($P < 0.05$) (see Table 2). In lung epidermoid carcinomas, four of five patients achieved PR at CF 9 mg/m^2, but only 1 of 21 at higher doses ($P < 0.05$) (see Table 3).

No therapeutic responses were seen in the following tumor types: colorectal (six patients), kidney (five patients), soft-tissue sarcoma (four patients), cervix (four patients), melanoma (two patients), astrocytoma (one patient), esophagus (one patient), vulva (one patient).

Table 2. Therapeutic effect of DDMP 90 mg/m^2 and delayed CF administration (24 h) in head and neck cancer

CF dose (mg/m^2)	Number of patients	PR
9	9	5
15	2	2
20	5	0
30	3	0
45	3	0
108 (9 × 12)	5	1
Total	27	8 (~ 30%)

Table 3. Therapeutic effect of DDMP 90 mg/m^2 and delayed CF administration (24 h) in lung epidermoid cancer

CF dose (mg/m^2)	Number of patients	PR
9	5	4
15	3	0
20	1	0
30	3	0
45	5	1
108 (9 × 12)	9	0
Total	26	5 (~ 19%)

Toxicity

As for therapeutic response, hematologic toxicity was inversely related to CF dose level (see Tables 4 and 5). Thrombocytopenia was more severe than leukopenia. At 9 mg/m^2, severe thrombocytopenia (platelets < 50,000) was seen in 17 of 29 courses. Twelve patients had platelet levels (< 20,000/mm^3) so low as to require platelet transfusion in addition to CF rescue. In two cases, toxicity contributed to death secondary to sepsis and bleeding. With CF doses above 20 mg/m^2 no toxicity was seen.

Other toxic effects included a morbilliform rash that often preceded severe hematopoietic toxicity by 24–48 h. Gastrointestinal toxicity: nausea/vomiting and/or diarrhea, was seen in one-third of patients and was easily controllable. No CNS toxicity was encountered.

Discussion

In this study DDMP has demonstrated therapeutic activity in epidermoid carcinomas of head and neck and of lung. For a given dose of DDMP, this effect is inversely related to the dose level of CF and cannot be dissociated from hematologic toxicity. Increasing the dose of CF clearly results in the loss of therapeutic activity. There is no evidence of a selective protection of the bone marrow.

The comparison between concomitant and delayed CF administration has been investigated in a later prospective randomized trial by the EORTC Early Clinical Trials Group.

Since very few patients had received prior treatment with MTX, no answer is given to the important question of cross resistance between MTX and DDMP. This remains a central issue, since the future clinical role of DDMP may be in selected cases of MTX resistance, in addition to which it has a potential use for compartmental chemotherapy in neoplastic diseases of the CNS and meninges.

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Table 4. Bone marrow toxicity: Leukocyte nadir after DDMP 90 mg/m^2 and delayed CF administration

CF dose (mg/m^2)	Number of courses	Leukocyte nadir/mm^3			
		> 4,000	4,000 to 2,000	2,000 to 1,000	< 1,000
9	29	15	9	3	2
15	14	8	3	3	–
20	20	15	4	1	–
30	27	27	–	–	–
45	26	25	1	–	–
108 (9 × 12)	19	19	–	–	–

Table 5. Bone marrow toxicity: Platelet nadir after DDMP 90 mg/m^2 and delayed CF administration

CF dose (mg/m^2)	Number of courses	Platelet nadir × 10^3/mm^3			
		> 100	100 to 50	50 to 20	< 20
9	29	9	3	5	12
15	14	6	3	2	3
20	20	14	3	1	2
30	27	27	–	–	–
45	26	25	–	1	–
108 (9 × 12)	19	18	1	–	–

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