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5-Fluorouracil in the treatment of scleroderma: a randomised, double blind, placebo controlled international collaborative study

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Abstract

A six month controlled study of 5-fluorouracil in the treatment of scleroderma showed a modest benefit in skin scores, Raynaud's phenomenon, and patients' global assessment. Visceral organ and hand function were unaffected. Mild to moderate toxicity was common in the 5-fluorouracil treated patients but usually responded to dose reduction. Two patients receiving 5-fluorouracil died from causes seemingly unrelated to treatment. Significant clinical improvement in scleroderma was not noted in the first six months of treatment with 5-fluorouracil.

Pharmacological treatment directed at preventing or reversing tissue fibrosis in scleroderma has been largely ineffective.[1 2] D-Penicillamine is a possible exception, but benefits occur slowly, are often minimal, and treatment is commonly limited by toxicity.[3 4]

Based upon the clinical observations that topical 5-fluorouracil was efficacious in the treatment of plantar fibrosclerosis and that the skin manifestations of scleroderma improved after combination chemotherapy with methotrexate, cyclophosphamide, and 5-fluorouracil given for breast cancer, an open label unblinded study of 12 patients with scleroderma was made.[5] Based upon the results in that preliminary study, a double blind, randomised, placebo controlled study was conducted to evaluate critically the efficacy of 5-fluorouracil in the treatment of scleroderma.

Materials and methods

An international collaborative study was undertaken between doctors at the Universidad Peruana Cayetano Heredia in Lima, Peru (UPCH) and the University of Alabama at Birmingham in Birmingham, Alabama, USA (UAB). Patients with scleroderma, as classified and defined by the American Rheumatism Association criteria,[4] were identified and after informed consent randomly assigned to treatment with 5-fluorouracil or placebo. The protocols at both institutions were virtually identical and randomisation was conducted separately at each institution. Patients with limited scleroderma were enrolled only if there was evidence of visceral disease or digital ulcerations, which would permit an assessment of improvement. None of the patients studied had received D-penicillamine within six months of the start of this trial and none had received colchicine at any time. Corticosteroids were permitted for the treatment of steroid responsive inflammatory conditions, including myositis and pericarditis. All female patients were either postmenopausal or using effective contraceptive methods at the time of the study.

Clinical and laboratory evaluations were conducted at baseline, three and six months, or at study completion. Both patients and doctors were unaware of the study medication. Assessment was performed in a manner similar to that in the open trial.[5] Skin and musculoskeletal systems assessment included the following: (*a*) total skin score as developed by Medsger *et al* (maximum score 104)[6]; (*b*) maximal oral opening, in mm; (*c*) flexion index (distance between the third proximal interphalangeal joint and the distal palmar crease with the hand in full flexion, in mm); (*d*) extension index (distance between the third fingertip and the distal palmar crease with the hand in full extension, in mm); (*e*) functional index as developed by Guillevin and Ortonne[1] (which evaluates 11 activities of daily living likely to be affected in patients with scleroderma); (*f*) measurement of skin ulcers; (*g*) 7 mm skin punch biopsy for wet weight (taken from the ventral aspect of the lower third of the forearm and performed at baseline and six months); and (*h*) frequency and severity of Raynaud's phenomenon.

In addition to a complete history and physical examination, vascular and visceral disease were assessed by the following tests performed at baseline and six months: chest radiographs and pulmonary function testing (including diffusion capacity and arterial blood gases); serum creatinine, urine analysis, 24 hour urine for protein and creatinine clearance; electrocardiogram and echocardiograms; and oesophageal manometry. Vascular and visceral disease (including Raynaud's phenomenon, oesophageal, pulmonary, cardiovascular, renal, and muscular involvement) were recorded as either mild, moderate, or severe and given numerical values (1, 2, or 3) for computation purposes at both baseline and follow up in the same manner as in the open trial.[5] Global assessments were obtained at the end of the infusions and three months later. Patients were asked whether they felt they had benefited from participating in the study. Patients who claimed they had worsened or had not changed were given a score of 0. Those who improved were graded as mild, moderate, or significant improvement and given scores of 1, 2, and 3 respectively. The most conservative of the two responses was used for computation purposes. Laboratory evaluations included a complete blood count and chemistry profile.

The patients were treated intravenously with 12 mg/kg daily of 5-fluorouracil for four doses, followed by four additional doses (6 mg/kg not

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to exceed 800 mg) given intravenously every two days (inductive phase). This was followed by a weekly dose of 12·5 mg/kg intravenously (maintenance dose). No single dose at any time exceeded 1000 mg. A clinical evaluation and complete blood count were performed before each dose. The dose was reduced by 25% for any of the following reasons: (*a*) the white blood cell count dropped by ≥50%; (*b*) leucopenia (total white blood cell count 4×10^9/l); (*c*) mucositis; or (*d*) severe nausea, vomiting, or diarrhoea. Patients randomly assigned to placebo received an intravenous infusion similar in appearance to 5-fluorouracil. Both 5-fluorouracil and placebo infusions were given by a registered nurse; both the assessors and the patients were unaware of whether the patient had received 5-fluorouracil or placebo.

To detect 30% differences between the study drug and placebo, and considering an attrition rate of 20%, an $\alpha=0{\cdot}05$, and a $\beta=0{\cdot}80$, a sample size of 60 was estimated.

Measurements performed at different times during the treatment were compared using either the Student's *t* test or the χ^2 distribution (with Yates's correction where appropriate). To compare the skin scores they were converted into percentages; the total skin score was considered changed (improved or worsened) at six months if it was at least four points and 10% different from that at baseline. In all cases a p value ≤0·05 was chosen as indicative of significance.

*Table 1 Demographic and selected clinical features of patients with scleroderma studied**

Feature	Treatment group	
	Placebo (n=20)	5-Fluorouracil (n=26)
Mean (SD) age years	42·9 (15·7)	43·7 (15·8)
No (%) female	20 (100)	23 (88)
No (%) Mestizo	17 (85)	19 (73)
Mean (SD) duration of disease (years)	5·04 (4·6)	5·01 (4·1)
Mean (SD) total skin score	24·2 (15·8)	34·0 (15·6)
Mean (SD) skin weight (g)	25·2 (12·9)	34·6 (16·3)
Mean (SD) Raynaud's score	1·95 (0·9)	1·70 (0·9)
Mean (SD) oral opening (mm)	38·1 (10·2)	41·0 (8·0)
Mean (SD) ulcer (number)	0·95 (1·1)	0·80 (1·2)
No (%) with complications		
Oesophageal involvement	15 (75)	18 (69)
Lung involvement	16 (80)	19 (73)
Heart involvement	11 (55)	16 (62)
Muscle involvement	2 (10)	2 (8)
No (%) receiving		
H_2 blockers	2 (10)	3 (12)
Calcium channel blockers	2 (10)	4 (15)
Prednisone	3 (15)	2 (8)

*All comparisons not significant except for total skin score (p=0·04).

Table 2 Differences between evaluations performed at six months and at enrolment in patients with scleroderma studied.† Values are means (SD)

Feature‡	Treatment group	
	Placebo (n=20)	5-Fluorouracil (n=26)
Total skin score*	−1·7 (3·4)	−5·8 (1·4)
Skin weight (g)	−0·7 (1·6)	−3·7 (3·8)
Oral opening (mm)	−1·4 (3·8)	−0·2 (0·8)
Flexion index (mm)	−2·2 (2·3)	−0·7 (0·7)
Extension index (mm)*	−0·65 (0·10)	−2·2 (0·5)
Functional score	−3·3 (0·66)	−2·1 (1·3)
Global assessment**	0·9 (0·78)	1·52 (0·91)
Raynaud's score*	0·0 (0·04)	−0·44 (0·18)
Ulcer (number)	0·25 (0·18)	−0·1 (0·2)
Oesophageal involvement (score)	−0·1 (0·16)	0·0 (0·0)
Lung involvement (score)	0·2 (0·08)	−0·2 (0·01)
Heart involvement (score)	0·15 (0·01)	−0·23 (1·03)
Muscle involvement (score)	0·0 (0·0)	0·04 (0·01)

*p<0·05; **p<0·02.
†Values are expressed as the mean differences between six months and enrolment.
‡See text for explanation of features.

Results

Of 70 patients enrolled in the study, 33 patients received placebo and 37 the study drug. Twenty patients receiving placebo and 26 patients receiving 5-fluorouracil completed the study. The reasons for drop out in the placebo group were lack of compliance or improvement, or both, in eight patients, events unrelated to the treatment (pneumonia and empyema) in one patient, and four patients moved outside the study area. In the group receiving 5-fluorouracil, seven patients dropped out because of lack of compliance or improvement, or both, two with events unrelated to treatment (both died, see below), and two moved outside the study area. The dropout rate for the patients receiving placebo and 5-fluorouracil (39% *v* 30%) was comparable, as was the dropout rate at the two collaborating institutions at Lima and Alabama (31% *v* 44%).

Parameters were studied at baseline and at six months. Patients in both study groups were comparable at baseline except for a significantly higher total skin score in the group receiving 5-fluorouracil (table 1). Patients were also comparable at baseline at both locations. Statistically significant improvement was observed in the group receiving 5-fluorouracil compared with those receiving placebo for the following indices: total skin score, extension index, patients' global assessment, and Raynaud's score (table 2). In the group receiving 5-fluorouracil the proportion of patients whose skin scores improved between 10% and 19%, 20% and 29%, or more than 30% was 4%, 24%, and 28% respectively with a mean overall percentage (SD) improvement of 31·1 (8·8)%. For the same group 20% of patients had a worse total skin score with a mean percentage (SD) worsening of 27·6 (10·8)%. These results contrast with those found in the placebo group, in which the proportion of patients whose skin score improved by the same percentages were 21%, 5%, and 0% respectively, with a mean overall percentage (SD) improvement of 16 (4·3)% (p<0·001 compared with the group receiving 5-fluorouracil). For the placebo group the proportion of patients whose skin score worsened was 26% but the mean percentage (SD) worsening was 54·2 (40·5)% (p=0·08) compared with the group receiving 5-fluorouracil.

Toxicities were more likely to occur in the group receiving 5-fluorouracil (p=0·001) (table 3). The dose was modified in 11 of the 26 patients receiving 5-fluorouracil who completed the trial but only in one of the 20 patients receiving placebo who completed the trial (p<0·01). Two patients, both receiving 5-fluorouracil, died. One patient developed thrombotic thrombocytopenic purpura and died with a massive intracranial haemorrhage despite aggressive treatment.[7] The other patient died of cardiorespiratory failure in association with diffuse and rapidly progressive scleroderma, unaffected by 5-fluorouracil treatment.

Table 3 No (%) of side effects noted in the patients with scleroderma studied

Events	Placebo (n=20)		5-Fluorouracil (n=26)	
	No	%	No	%
Haemocytopenia	1	5	12	46
Leucopenia*	1	5	11	42
Thrombocytopenia†	0	0	1	4
Gastrointestinal symptoms‡	8	40	25	96
Angina pectoris	0	0	1	4
Pruritus	0	0	1	4
Total§ (patients)	10	50‖	39 (25)	96‖

*White blood cell count $<4\times10^9$/l at lowest point.
†One patient had a platelet count of 102×10^9/l at lowest point.
‡Nausea, vomiting, or diarrhoea as reported by the patient.
§Number of events per study group.
‖p=0·001.

Discussion

The results of this study suggest that 5-fluorouracil has a modest benefit in some patients with scleroderma. Skin scores improved in a larger proportion and in a higher percentage of 5-fluorouracil treated patients than placebo treated patients. Improvement in patients' global assessment seemed to reflect the changes in the skin score and Raynaud's phenomenon, but functional indices and visceral organ functions were largely unaffected by treatment. These findings support the interpretation that the benefits noted resulted only in modest clinical benefit. It is not known whether treatment for longer periods of time would result in improved hand or visceral organ function. The six month study period was chosen because of observations in the initial study and owing to financial constraints. The results were similar for patients with disease duration of ≤24 months, though the small number would make the chance of a β error considerable.

One patient receiving 5-fluorouracil noted improvement in severe myalgias that had been a feature of her scleroderma, whereas two others, one receiving 5-fluorouracil and the other placebo, did not.

Toxicity was common in patients treated with 5-fluorouracil. Gastrointestinal symptoms were noted in 25 (96%) of 26 patients receiving 5-fluorouracil compared with 8 (40%) of 20 receiving placebo. These symptoms generally responded to dose reduction and no patient was removed from the study because of gastrointestinal toxicity. The fact that a significant proportion of the placebo treated patients had gastrointestinal symptoms prevented the assessors, who were unaware of the blood counts, from guessing correctly which drugs the patients were receiving, and thus preserved the 'blind' nature of this clinical trial.

Haemocytopenias were noted in 12 (46%) of the patients receiving 5-fluorouracil compared with 1 (5%) of those receiving placebo. Leucopenia was most common but was never $<3\times10^9$/l and did not result in any infection. This too responded to dose reduction and no patient was removed from the study for this toxicity. Mild thrombocytopenia occurred in one patient receiving 5-fluorouracil but resolved uneventfully. Severe thrombocytopenia occurred in another patient not included in the analysis as she did not complete this study. She developed this complication two weeks after a dose of 5-fluorouracil and eventually died. This patient clinically had thrombotic thrombocytopenic purpura, which has not been previously reported in patients receiving 5-fluorouracil or who had scleroderma, and is being reported separately.[7]

One patient receiving 5-fluorouracil developed angina pectoris, which is an uncommon complication of this drug.[8–12] Another patient receiving 5-fluorouracil died of cardiorespiratory failure, present before treatment was started. Although 5-fluorouracil has been reported to cause profound but reversible heart failure,[12] the role of this drug in this patient's clinical course and eventual demise can only be surmised. One patient receiving 5-fluorouracil developed mild pruritus, which subsided without change of dose.

The dosing regimen in this study differed slightly from that in the preliminary study. A total of 1000 mg was the maximum single dose prescribed in this study in conformity with the manufacturer's recommendation.[13] This limit was not applied in the preliminary study. It is doubtful that this small change significantly altered the efficacy of the drug.

In summary, this study showed modest benefit for 5-fluorouracil in scleroderma, but no improvement in function or visceral organ disease. Mild toxicity was common and responded to dose reduction. Two patients receiving 5-fluorouracil died, one from thrombotic thrombocytopenic purpura, which seemingly was unrelated to treatment with 5-fluorouracil, and the other from progressive heart failure, probably secondary to scleroderma. It is not known whether a longer duration of treatment or treatment confined to patients with no more than two years of disease would yield different results.

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