A new promising treatment in systemic sclerosis: 5-fluorouracil

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SUMMARY Twelve patients with systemic sclerosis according to American Rheumatism Association criteria were treated with intravenous 5-fluorouracil. Significant subjective and objective improvement occurred initially in the skin and subsequently in the involved viscera and vasculature. These preliminary results suggest that 5-fluorouracil may be an effective treatment for systemic sclerosis.

Systemic sclerosis is a disease of unknown aetiology, characterised by induration and thickening of the skin. It is frequently associated with Raynaud's phenomenon and organ-system involvement including the gastrointestinal tract, lungs, heart, and kidneys.1 There are an estimated 2–12 new cases/million/year, which is approximately 30 000 new cases a year worldwide. The natural course of the disease varies; complete remission occurs infrequently. Organ-system involvement is responsible for significant morbidity and mortality. A cumulative survival of 65% at two years and 35% at seven years from disease onset has been reported in one study, whereas, in another, 20% of affected individuals were alive 10 years after disease onset.2,3

More than 50 drugs have been tried as treatment for this disease.4–6 These drugs included non-steroidals, sex and adrenal corticosteroids, immunosuppressors, antifibrotics, and others. Most of these agents have proved to be non-efficacious, with the possible exception of d-penicillamine, which may produce skin improvement and halt the progression of visceral involvement. These changes are relatively slow to appear, however, and the drug has definite and important side effects.4,7

The observations by one of us (CPS) of the efficacy of topically applied 5-fluorouracil (5-FU) in the treatment of a patient with plantar fibrosclerosis, and of improvement of skin manifestations in another patient with scleroderma after treatment with combination chemotherapy (methotrexate, cyclophosphamide, and 5-FU) for breast cancer, prompted us to try this drug parenterally in one patient who presented with diffuse and rapidly progressive scleroderma. This patient responded dramatically to this treatment regimen and represents the first of the 12 cases presented in this report.

Patients and methods

The study was conducted in 12 patients with progressive systemic sclerosis (scleroderma) at the Arzobispo Loayza Hospital in Lima, Peru. All patients were female and either postmenopausal or using effective contraceptive methods at the time of the study. Written informed consent was obtained before participation.

Clinical evaluation was conducted by one of us (JAC) and included assessment of the skin and musculoskeletal systems as follows: (a) total skin score (TSS) as developed by Medsger et al (maximum score 104)8; (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 fingertips and the distal palmar crease with the hand flexion, in mm); (e) palmar impression (or hand print; obtained in the same manner as a finger print it objectively demonstrates an improvement in hand extension: the palmar impression becomes larger); (f) range of motion of affected joints (most commonly elbows and wrists); and (g) functional index as developed by Guillevin and Ortonne9 (which evaluates 11 activities of daily living likely to be
affected in patients with scleroderma) (see Appendix).

In addition to a complete history and physical examination, evaluation for vascular and visceral involvement included the following tests done serially: chest radiographs and pulmonary function testing; urine analysis, 24 hour urine for protein and creatinine clearance; electrocardiograms (ECG) and MUGA scans and barium swallows. Vascular and visceral involvement (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 visits (refer to Table 1 for definitions of mild, moderate, and severe).

The patients were treated intravenously (IV) with 12.5 mg/kg/day of 5-FU for four to five doses, followed by four additional doses (8-10 mg/kg) given IV every two days (inductive phase). This was followed by a weekly dose of 10-20 mg/kg IV (maintenance dose). Therapy was monitored with a complete blood count and a clinical evaluation before each dose. While treated with 5-FU our patients did not receive other pharmacological agents, such as H2 blockers, corticosteroids, calcium channel blockers, and/or cytotoxics, which could have conceivably influenced the course of their illness.

Measurements performed at different times during the treatment were compared using non-parametric statistical tests. A p value ≤0.05 was chosen as indicative of statistical significance.

**Table 1  Scoring system for vascular and visceral involvement in patients studied**

<table>
<thead>
<tr>
<th></th>
<th>Mild (1)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud's</td>
<td>Less than five times/day</td>
<td>More than 15 times/day or digital ulcerations, or both</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Dysphagia to some solid foods. Normal barium swallow</td>
<td>Dysphagia to solid and soft foods and weight loss (&gt;10% pre-illness weight). Abnormal barium swallow with dilatation of the lower two thirds of the oesophagus</td>
</tr>
<tr>
<td>Lung</td>
<td>No symptoms: vital capacity &gt;70% predicted and CO diffusing capacity between 50 and 75% of predicted. P02 &gt; 80 mmHg</td>
<td>Dyspnoea plus vital capacity &lt;50% of predicted or CO diffusing capacity &lt;33% of predicted, P02 &lt; 60 mmHg</td>
</tr>
<tr>
<td>Heart</td>
<td>Non-specific ST-T changes</td>
<td>Angina, definite ischaemic changes by ECG*, hypokinesis by MUGA scan or an ejection fraction &lt;30%</td>
</tr>
<tr>
<td>Muscle</td>
<td>Mild EMG* or CK* abnormalities</td>
<td>Definite myositis clinically, biochemically, by EMG or by muscle biopsy</td>
</tr>
<tr>
<td>Renal</td>
<td>Mild hypertension, or a serum creatinine 1.5x normal, or a creatinine clearance &gt;80% or a 24 hour protein of &lt;500 mg</td>
<td>Refractory hypertension, or a serum creatinine 4x normal, or a creatinine clearance &lt;20%, or a 24 hour protein &gt;3 g</td>
</tr>
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</table>

**Results**

The demographic and clinical characteristics (at baseline and last visit) of the 12 patients studied are listed in Table 2. To better illustrate our report the course of the first three patients is presented here in some detail. Duration of treatment ranged from 1 to 20 months. Nine patients received 5-FU for at least six months.

**PATIENT NO 1**

A 28 year old woman presented with severe dysphagia, an 8 kg weight loss, Raynaud's phenomenon, diffuse scleroderma, and severe constipation (unresponsive to laxatives) of five months' duration. Shortly after initiating 5-FU she noticed decreased induration of her skin which was objectively shown by a decrease in the TSS (from 49 at baseline to 30, three months later). By the fourth month her constipation, dysphagia, and Raynaud's phenomenon had resolved. One year after initiating this treatment she discontinued the 5-FU for financial reasons. Her constipation recurred. She resumed treatment with 5-FU and has remained asymptomatic. She has regained weight and is receiving maintenance treatment with 5-FU as described.

**PATIENT NO 2**

A 24 year old woman presented with diffuse scleroderma of seven months' duration and significant pulmonary involvement characterised by progressive dyspnoea on exertion. She also had decreased range of motion (owing to skin...
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involvement) of the neck, shoulders, and elbows. Four weeks after the onset of treatment with 5-FU there was marked improvement in her skin and improved range of motion of the affected joints. By the fourth month of treatment her shortness of breath had subsided, and her CO diffusing capacity and vital capacity had improved from 30 to 82% and from 78 to 89% of predicted respectively. Fig. 1 depicts her clinical course.

**Patient No 3**

A 42 year old woman with diffuse scleroderma of 18 months' duration presented with marked skin involvement, severe dysphagia, interstitial pulmonary disease, angina, an abnormal ECG, areas of hypokinesis by MUGA scan, and an ejection fraction of 15%. She also had EMG changes diagnostic of myopathy. One month after starting 5-FU she experienced decreased induration of her skin and improved range of motion of the affected joints. Unfortunately, she developed aspiration pneumonia complicated by an empyema and, despite supportive therapy, died of cardiorespiratory failure five weeks after the initiation of 5-FU. While in hospital her white blood cell count and differential remained within normal limits.

**Patients 4–12**

The remaining nine patients enrolled in the study showed similar patterns of response to this treatment. By the end of the first or second week they noticed decreased skin thickening and during the subsequent four to six week there were objective changes shown by a decrease in the TSS (mean 36.5...
at baseline; 22.0 at last visit; p=0.01), an increase in
the oral opening (mean 31.3 mm at baseline; 33.5 at
last visit; p=NS), and improvement in the flexion
index (mean 98.5 mm at baseline; 92.6 at follow up;
p=NS) and extension index (mean 140.1 mm at
baseline; 146.4 at follow up; p=NS). By week 8–10
there was definite improvement of their Raynaud's
phenomenon. The mean Raynaud’s score was 2.2 at
baseline compared with 1.3 at the last visit
(p=0.035). Two patients had healing of digital
ulcers. The mean oesophageal score was 1.6 at
baseline compared with 0.8 at the last visit
(p=0.07). The mean pulmonary score was 1.8 at
baseline compared with 1.2 at the last visit
(p=0.10). The mean functional index was 12.4 at
baseline and 6.5 at the last visit (p=0.026). In
general, the response appeared to be related to the
severity of the disease and its duration, i.e., the
worse the symptoms and the shorter the duration,
the more beneficial the treatment.

Of the 487 doses that our 12 patients were
supposed to receive, 77 were not administered; 12
doses could not be given owing to transient un-
availability of 5-FU, and the remaining 65 owing to
the patients’ inability to come to the hospital. It
should be noted that seven of the 12 patients
continue to receive 5-FU. One patient died (patient
No 3, described in detail: patient died of aspiration
pneumonia), and the remaining four were lost to
follow up 3, 6, 11, and 15 months after starting 5-FU
(patients Nos 7, 9, 4 and 2 respectively). 5-
Fluorouracil was discontinued temporarily in almost
all patients (one or two doses). Two patients (Nos 7
and 4) stopped 5-FU for a few weeks. This was
followed by reappearance of digital ulcerations.

SIDE EFFECTS
In general, patient tolerance of 5-FU was very good.
Side effects included mild upper gastrointestinal
symptoms in seven patients, which were self limited
or resolved by a change in dosing from IV bolus to
IV infusion or a dose reduction of 25%, or both.
Two patients developed mild transient leucopenia at
the end of the inductive phase of treatment that
resolved when the interval of administration was
increased. One patient experienced an intense
headache during the infusion of his 17th dose,
however this did not recur with subsequent doses.

Discussion
It is very difficult to draw conclusions about the
benefit of any drug treatment in scleroderma given
the variable course of this disease.1 2 Additionally,
this study was not carried out blind and was
uncontrolled. Our scoring system for vascular and
visceral involvement uses subjective and objective
criteria; these criteria were chosen not only because
of their availability in the clinical setting where our
patients were studied, but also because of their
reliability and relative clinical importance in this
disorder as noted by other investigators.3 We failed,
however, to obtain serial skin biopsy specimens,
which could have helped in the objective evaluation
of skin involvement. A consistent pattern of re-
response to therapy with 5-FU was seen in these 12
patients and suggests a causal relation between
improvement and treatment. Even those patients
with the most severe form of the disease responded.
Improvement was noted early, and began with, but
was not limited to the skin, as it included vascular
and visceral organs as well. When the treatment was
interrupted for whatever reason, the skin changes
(including digital ulcerations) recurred. These
changes responded to reinstitution of therapy with
5-FU and were not felt to be related to seasonal
temperature changes. We do not yet know how
long 5-FU should be administered (at maintenance
dose), but six months appear to be reasonable
before considering the trial a failure; if a patient
continues to improve, however, a longer trial could
be justified. Because systemic sclerosis remains a
difficult disease to treat effectively we believe that
our experience, although preliminary, deserves re-
porting.

If proved effective, the mechanism of action of
5-FU in this disorder remains to be determined. It
can be speculated that 5-FU could prevent the
differentiation of endothelial and periendothelial
cells into fibroblast and thus the active deposition of
collagen.10 It is conceivable that other mechanism(s)
could be operative as patients with more severe
disease of shorter duration appear to do better, but
even patients with longstanding disease may show
some improvement.

Because of these preliminary data we are conduct-
ing a double blind study in patients with newly
diagnosed scleroderma at both collaborating institu-
tions.

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Appendix Functional index

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>without any difficulty.</td>
</tr>
<tr>
<td>1</td>
<td>with some difficulty.</td>
</tr>
<tr>
<td>2</td>
<td>with great deal of difficulty.</td>
</tr>
<tr>
<td>3</td>
<td>unable to do.</td>
</tr>
</tbody>
</table>
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Activities:
1. Pick up a bottle with one hand.
2. Lift a glass from the table to your mouth.
3. Turn a door knob.
4. Turn a key in keyhole.
5. Open a drawer.
6. Cut your food (using fork and knife).
7. Spread butter on your bread.
8. Hold a teaspoon.
9. Chew your food.
10. Wind your watch.
11. Write.

References