Razoxane in treatment of acute myeloid leukaemia

Razoxane (ICRF 159; 1,2-Bis (3,5 dioxopiperazin-1-yl) propane, C₁₁H₁₆N₄O₄) has been used for treating acute leukaemia.¹ It is thought to act as an inhibitor of RNA, or more likely of DNA, and to interfere with cell division at the G₂/M phase of the cell cycle.² After recent claims of success with razoxane and cytosine in treating acute myeloid leukaemia and the relative absence of side effects, we decided to treat consecutive and unselected patients with acute myeloid leukaemia with this combination.

Patients, methods, and results

Seventeen consecutive cases seen by us between October 1977 and February 1978 were included in the study. There were 10 adults with acute myeloblastic leukaemia (age range 35-78), of whom two had been previously treated and were resistant to other cytotoxic drugs; five cases of acute myelomonocytic leukaemia (age range 14-82); and two cases of chronic granulocytic leukaemia (CML) in blast transformation (age range 29-39).

Razoxane was given by mouth in a dose of 125 mg three times daily, and cytarabine intravenously in a daily dose of 1 mg/kg body weight. Both drugs were given for three consecutive days and the course repeated at ten-day intervals. When no satisfactory response was achieved the dosage was increased to 125 mg razoxane four times a day and cytarabine to 2 mg/kg body weight/day.

Effect of razoxane and cytarabine on blast, platelet, and neutrophil counts after one course.

We obtained poor remission results. Thirteen of the 17 patients died. None of these patients had more than four courses of treatment. The main cause of death was haemorrhage or septicæmia. Of the four patients who are alive, only two entered remission. One of these did not respond to five courses initially but remission was obtained after four courses at the higher dosage. In the other patient bone marrow aspiration was difficult because of the presence of reticulins. After nine courses she was judged to be in remission by her excellent clinical condition and normal peripheral blood count, but confirmation by bone marrow examination is lacking. Both these patients remain well on maintenance treatment.

The two patients with CML in acute blast transformation remained reasonably well initially. One of them could not tolerate further treatment owing to severe nausea and vomiting and treatment was discontinued. The other has remained well with this combination and has received 12 courses of treatment altogether. It is now 27 weeks since blast transformation was first diagnosed. She requires transfusions every 10 days but apart from that has no haemorrhagic or infective complications.

The total white cell count, platelets, and the blast count in the peripheral blood dropped after the first course of treatment (figure). With subsequent courses the neutrophil count rose moderately. Platelet counts fell progressively with each course of treatment with no subsequent rise, except in the two patients who entered remission.

Every patient complained of nausea and vomiting of varying severity. One patient complained of calf pain related to treatment, but the blood urea and electrolyte concentrations and the results of neurological examination were normal. None of our patients developed alopecia.

Comment

These results indicate that when used in this way razoxane is not satisfactory treatment for acute myeloid leukaemia. We would recommend that it should only be used when other regimens have failed. Although remission was achieved in one (possibly two) cases, the dose of cytarabine was such that the remission could have been due to that drug alone. Our response and remission rates were no better than those previously obtained in this department using cytarabine alone.³

The results obtained in CML in blast crisis were encouraging. Since the results of treatment in this group of patients is usually unsatisfactory, further trials with razoxane in combination with cytarabine and other drugs known to be partially effective in this disease—for example, vincristine—should be undertaken.

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Factors inducing relapse in inflammatory bowel disease

It is common clinical experience that events such as upper respiratory tract infections, emotional disturbances,¹ and gastroenteritis² may well precede an attack of either ulcerative colitis (UC) or Crohn's disease (CD). No formal study has been performed previously to confirm these clinical impressions. We have therefore attempted to investigate the role of various possible triggering factors in inducing relapses in patients with both UC and CD.

Methods and results

A total of 38 patients with UC and 30 patients with CD were studied over six months. For the patients with UC this resulted in a total of 59 outpatient attendances and for the patients with CD a total of 61 outpatient attendances. The extent and severity of disease and length of history were recorded. Each patient was asked whether during the previous month he or she had taken antibiotics or had suffered from one or more of the following factors: infections, atopy, emotional crises, or dietary indiscretions. All patients were questioned in this way at each outpatient attendance during the six months, irrespective of their clinical state. If patients were seen in the clinic less than one month after the previous visit then the observations for the second attendance were not included in the final analysis. The data were analysed using a χ^2 test.

For patients with UC 15 relapses were observed during the 59 clinic attendances. Of these 15 relapses, 13 were associated with the occurrence of one of the possible precipitating factors in the month before the clinic appointment (table). Of 44 attendances while the patients were in remission, only 12 were associated with a precipitating factor. The difference is highly significant ($P < 0.0005$). Of these precipitating factors, the vast majority for

Relapse related to precipitating factor

	Presence of precipitating factor in previous month		Total	Statistical analysis
	No	Yes		
<i>Ulcerative colitis</i>				
Relapse	2	13	15	$\chi^2 = 16.16$ $n = 1$ $P < 0.0005$
Remission	32	12	44	
Total	34	25	59	
<i>Crohn's disease</i>				
Relapse	5	13	18	$\chi^2 = 12.95$ $n = 1$ $P < 0.0005$
Remission	33	10	43	
Total	38	23	61	

patients in both relapse and remission were upper respiratory tract infections (URTI). Other factors associated with relapse were stress (2), *Escherichia coli* urinary tract infection (1), and gastroenteritis (1).

For patients with CD, 18 relapses were observed during the 61 clinic attendances. Of these 18 relapses, 13 were associated with a precipitating factor (table). Of 43 attendances of patients with quiescent disease, only 10 were associated with a precipitating factor ($P < 0.0005$). Most of the precipitating factors were again URTIs. One patient who was in relapse had begun divorce proceedings in the previous month.

Even when upper respiratory tract infections were considered alone, patients with a relapse of either UC or CD were significantly more likely to have had an infection in the previous month than those in remission (UC relapse *v* remission $P < 0.01$, CD relapse *v* remission $P < 0.005$). No patient with an URTI had received an antibiotic during the previous month.

Comment

The present study has shown that there is a highly significant association between URTIs and a relapse of either UC or CD. Thus 60% of patients with UC with a relapse had had an URTI during the previous month compared with 22.7% of patients who presented in remission. A similar relationship was present in patients with CD. Of the other precipitating factors investigated, none appeared with sufficient frequency to enable meaningful results to be obtained.

The reasons why URTIs should be associated with a relapse of either UC or CD are uncertain. One hypothesis is that circulating immune complexes resulting from the infection may be deposited in the diseased intestine. In rabbits deposition of immune complexes in the colon may cause colitis.^{3,4} Since animals infected with upper respiratory tract viruses may have circulating complexes,⁵ similar complexes occurring in human URTI may localise to the diseased bowel and lead to a relapse.

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² Weinstein, L, *Gastroenterology*, 1961, **40**, 323.

³ Hodgson, H J F, *et al*, *Gut*, 1978, **19**, 225.

⁴ Mee, A S, *et al*, *Gut*, 1978, **19**, A443.

⁵ Blandford, G, *Lancet*, 1977, **2**, 136.

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Presumed ataxia-telangiectasia in a man

Ataxia-telangiectasia is a complex, multisystem genetic disorder.^{1,2} It is usually fatal from uncontrolled infection in adolescence, though it shows some variability in severity, age of onset, and rate of progression. We report an unusual case of the condition, resembling Friedreich's ataxia, in a man.

Case report

The patient is a 37-year-old Italian lawyer with two children, who has been diabetic from the age of 35. His parents were first cousins, and there had been consanguineous marriages in previous generations. From infancy he had had recurrent infective diarrhoea and subsequently recurrent respiratory and urinary infections. He had had two operations for hypospadias in infancy, but his early development had otherwise been normal. Neurological symptoms began in his late teens, with weakness and wasting beginning distally in legs, later spreading proximally. Progressive ataxia developed later, though on 30 October 1977 he still walked unaided. He complained of "hypersensitivity" of the skin of the feet and legs.

His paternal grandfather and great-grandfather had had progressive walking difficulty and required wheelchairs in old age. In 1976 his father, though asymptomatic, had impaired proprioceptive sensation in the legs and an absent left ankle jerk.

The patient had telangiectases in both popliteal fossae, gonadal atrophy, bilateral pes cavus, and normal intellect. He had fine, phasic horizontal nystagmus on lateral gaze bilaterally; the eye movements were otherwise normal, as were the remaining cranial nerves. There were no bulbar conjunctival lesions. The arms showed symmetrical mild intention tremor and

diminished tendon reflexes; the legs showed symmetrical weakness and wasting, mainly distally. Posterior column sensation was absent and spinothalamic sensation impaired in both legs below the knees; knee jerks were present, ankle jerks absent, plantar responses flexor. His gait was ataxic and Romberg's sign positive. There was no peripheral nerve hypertrophy.

Serum IgA was undetectable on repeated examination; IgG 12.45 g/l (normal 11.4 ± 1.7 g/l) and IgM 2.1 g/l (normal 1.0 ± 0.4 g/l). Serum α -fetoprotein 36 MRC units/ml (raised). Hb 13.4 g/dl, normal red cell indices and morphology (no acanthocytes); WBC $15.8 \times 10^9/l$, 86% polymorphs; platelets normal; ESR (Westergren) 108 mm in first hour. Blood concentrations of urea, creatinine and electrolytes, bilirubin, aminotransferases, alkaline phosphatase, and fasting calcium and phosphate were normal; fasting blood sugar 6.4 mmol/l; VDRL negative; serum folate 1.8 μ g/l, B₁₂ > 1000 ng/l. Fasting blood cholesterol and serum triglyceride concentrations were normal, as was lipoprotein electrophoresis. Urine contained 1 pus cell high-power field, no growth on culture. Chest x-ray film showed lingular consolidation; skull x-ray film was normal; electrocardiogram was normal.

Results of clinical neurophysiological studies are given in the table. Electromyography (concentric needle electrode) showed no spontaneous activity and no motor units under volitional control in the right extensor digitorum brevis. In the right tibialis anterior there were fibrillation potentials, positive sharp waves, and a reduced interference pattern on volition; motor units were of normal configuration but increased duration. The findings indicated a mixed motor/sensory axonal neuropathy. A gastrocnemius muscle biopsy done in 1976 in Italy showed non-specific changes.

Results of clinical neurophysiological investigations

		Terminal latency (ms)	Evoked potential duration (ms)	Evoked potential amplitude (μ V)	Conduction velocity (m/s)
Motor	L median	4.3	15.4	7000	64.1
	R ulnar	2.7	15.9	6500	50
	R lat popliteal	9.8	4.4	250	35.8
	R digit II	3.2	1.6	0.8	46.9
Sensory	R digit V	1.9	1.8	2.0	65.8
	R sural	..	..	..	..
Sensory nerve action potential not obtainable					

Comment

In our view the telangiectasia, deficiency of IgA, and raised alpha-fetoprotein concentration confirm the diagnosis of ataxia-telangiectasia. The onset of neurological symptoms was late, the course relatively benign, and the predominance of the peripheral neuropathy unusual. Cases have been reported with survival into the fifth decade,³ presumably owing to the increasingly effective treatment of infection. Evidence of cerebellar dysfunction in our patient was slight, but in one report⁴ cerebellar dysfunction was minimal at the age of 34. Usually cerebellar ataxia is the predominant neurological manifestation, beginning in childhood. Nevertheless, peripheral neuropathy⁵ certainly occurs in this condition and in our patient was the initial and predominant neurological manifestation.

The nature of the disorder present in previous generations is unknown but the pattern suggests pseudo-dominant inheritance due to multiple consanguinity since ataxia-telangiectasia is usually due to an autosomal recessive gene. Though our patient and his relatives possibly suffered from a previously unreported hereditary axonal neuropathy associated with telangiectasia, immune deficiency, and a raised serum α -fetoprotein concentration, on balance we believe that it was probably an atypical presentation of ataxia-telangiectasia.

This patient was referred to JNW by Professor Mario Manfredi, professor of neurology at the University of Rome. We thank him for permission to publish this report, and also for providing details of the histological findings in the patient's muscle biopsy specimen.

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