been incriminated as responsible for small-intestinal mucosal change, but these deficiencies were absent or only marginal in the present series.

If the reduced absorptive capacity of the upper jejunum in Indians is representative of the function of the whole small intestine, this finding may be of considerable nutritional importance, particularly for populations with an inadequate or only marginally adequate diet. Furthermore, if the observed defect of absorption is acquired, elucidation of the causative factors and their elimination could make a substantial contribution to improving the nutritional status of the community.

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Bleomycin in advanced squamous cell carcinoma: a random controlled trial

Report of Medical Research Council Working Party on Bleomycin*

British Medical Journal, 1976, **1**, 188-190

Summary

Bleomycin was compared with conventional cytotoxic drugs in the treatment of 70 patients with advanced squamous cell carcinoma; the primary deposit was in the head and neck in 50 patients and in the perineum or skin in 20. Thirty-four patients received bleomycin while 36 received other cytotoxic drugs. No significant difference was detected between the two groups either in the proportion showing tumour regression or in the survival rates. If bleomycin is to advance the treatment of squamous cell carcinoma it can be only in combination with other drugs or with radiotherapy.

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Introduction

An uncontrolled trial has confirmed that bleomycin has significant clinical activity, but the response of patients with various types of tumours to bleomycin alone was poor.[1] We therefore conducted a randomised controlled trial comparing bleomycin with other cytotoxic drugs to determine the drug's effectiveness in treating patients with squamous cell carcinoma.

Patients and methods

Patients with well-differentiated squamous cell carcinoma in the mouth, pharynx, larynx, oesophagus, perineum, or skin were eligible for entry to the trial. The tumour had either to be too far advanced for an attempt at curative surgery or radiotherapy or, as was more common, to have recurred after surgery or radiotherapy. Only those patients who had a reasonable expectation of life and were easily accessible for treatment and follow-up were selected.

On entry to the trial, after inquiry by telephone to the MRC Statistical Research and Services Unit, the patient was given bleomycin treatment or treatment with other drugs. Patients were randomly allocated to the two treatment groups after stratification according to the treatment centre, the sex, and the following subsites within the sites mentioned above: buccal mucosa, gums, hard palate, floor of mouth, tongue, oropharynx, nasopharynx, pyriform sinus, postcricoid, posterior pharyngeal wall, supraglottic, glottic, or subglottic regions, cervical oesophagus, intrathoracic oesophagus, vulva, penis, scrotum, and anal orifice.

In the bleomycin group our intention was to give bleomycin 30 mg intramuscularly twice a week to a total of 300 mg if this was tolerated. We allowed a reduction in dose for extreme age in a few patients, and the dose was modified for other reasons too (see table II). Most patients were treated as outpatients. In the other group the clinician in charge used the cytotoxic drug and regimen of his choice. In both groups further chemotherapy or radiotherapy could be given after failure of treatment. Patients in both groups received analgesics, blood transfusions, surgical procedures to relieve pain, or steroids as considered necessary. Routine chest radiographs and haematological and biochemical investigations were carried out on all patients before, during, and after treatment.

Results

Seventy patients entered the trial; their distribution between treatments according to tumour site, sex, and age is shown in table I.

TABLE I—*Site of tumour, age, and sex of patients admitted to trial*

	No of patients	Site of tumour								Age (years)						Sex	
		Month	Pharynx	Larynx	Oesophagus	Perineum	Ear	Skin	Maxillary antrum	30-39	-49	-59	-69	-79	≥80	Men	Women
Bleomycin	34	11	4	7	0	7	1	3	1	0	2	8	16	4	4	23	11
Other	36	10	6	8	0	7	1	3	1	1	2	9	12	9	3	25	11

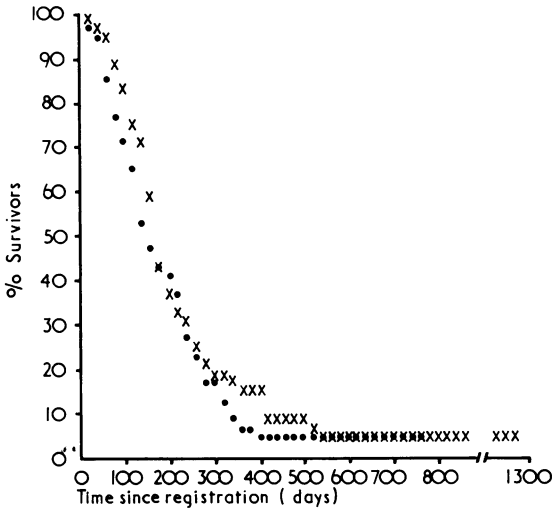
TABLE II—*Details of treatment and side effects in 34 patients taking bleomycin*

Dose (mg)	No of patients	Treatment modified	Reason for modification or side effects, or both
30	1	Yes	Died of lobar pneumonia 6 days after first injection
120	1	Yes	Patient unfit to attend clinic
120	1	Yes	Irritability and nausea, thickening of skin of fingers, did not return for follow-up after 120 mg
150	1	Yes	Ambulance strike
180	1	Yes	Very sore mouth: confined to irradiated area in floor
210	1	Yes	Weary and debilitated, sore mouth, finger erythema, stomatitis
210	1	Yes	Possible lung infiltration: received cyclophosphamide and prednisolone, too ill to follow-up possibility of lung infiltration
210	1	No	No further follow-up
225	1	Yes	Because of age (87), mild fever, erythema in right elbow
240	1	Yes	Painful ulcerations of skin, anorexia, blepharitis, and pruritis
240	1	Yes	Superficial ulceration of buccal mucosa, maculopapular lesions on both palms
255	1	Yes	3 weeks after first injection cheiropompholyx developed with arthralgia, then cellulitis around lesion (*Staph aureus*); treated with antibiotics, then cyclophosphamide
270	1	Yes	Received in two courses (120 and 150 mg) interrupted by failure to attend clinic, pyrexia
285	1	No	No side effects recorded
285	1	No	Anorexia, severe hair loss
300	16*	No	Peeling of skin on fingers (1); rash, diarrhoea, and vomiting (1); hair loss, pyrexia and shivering, pigmentation of elbows and shoulders, peeling of palms, tender finger pulp, sloughing of skin on legs (1); fever, elbow erythema, swelling hand joints (1); slight fever (1); reddening palms and elbows (1); glossitis and alpecia (1); shivering fits (1)
315	3	No	Severe hair loss, mild anorexia, generally unwell (1); slight peeling (1); pain at tumour site, change in hair colour (1)

*One patient received palliative *x*-ray treatment simultaneously.

TABLE IV—*Results of treatment in terms of change in size of tumour*

	No change	Increase	Marginal decrease	Definite decrease	Total
Bleomycin	12	2	5	4	23
Other	16	3	8	4	31



Percentage survival curves for patients on bleomycin (×) and patients on other drugs (●) obtained from standard life table calculations. Difference between the curves was not statistically significant (P>0·05).

Details of treatment in patients receiving bleomycin are shown in table II. The drugs taken by the other group are shown in table III. The original regimen had to be modified in four of these patients for the following reasons: one patient died of renal failure after a 100-mg intravenous dose of methotrexate; one developed pancytopenia on vincristine, cyclophosphamide, and methotrexate; one stopped taking cyclophosphamide because his condition deteriorated; and one was withdrawn from methotrexate (100 mg intravenously given only twice) and given palliative radiotherapy; no reason was given for this change. Three further patients taking cytotoxic drugs developed side effects that did not affect their treatment. Two developed neurotoxicity secondary to vincristine, and one also developed diarrhoea secondary to methotrexate; a third patient suffered leucopenia after cyclophosphamide.

The results of treatment in terms of tumour size, in the 54 patients in whom this could be measured, are given in table IV. No tumour regressed completely but the sites of origin of those tumours showing a definite decrease were: mouth (2), larynx (2), pharynx (2), and perineum (2). The survival curves for the two groups are shown in the figure and were compared by a log-rank test.[2] The difference between the two curves was not statistically significant (P>0·05).

No patient died from lung complications, and the extent of side effects necessitating withdrawal of drugs was broadly similar in both groups.

Discussion

An earlier report[1] of bleomycin treatment in an uncontrolled series confirmed the clinical activity of bleomycin and detailed the side effects of the drug. Halnan *et al* noted that the "quality and duration of response to bleomycin, used as a single agent, was poor" but they hoped that it might prove more effective than other cytotoxic drugs for squamous carcinoma. This present random controlled trial, however, has failed to show any statistically significant difference between bleomycin and other cytotoxic drugs either in terms of tumour regression or in prolonging survival. de Palo *et al*[3] carried out a similar trial to compare methotrexate with bleomycin in advanced epidermoid carcinoma of the uterine cervix. They also failed to show any significant difference between the two drugs.

Hence if bleomycin is to advance the treatment of squamous cell carcinoma probably it can only be in combination with

TABLE III—*Drugs taken by 36 patients not receiving bleomycin*

	Cyclophosphamide	Cyclophosphamide and vincristine	Methotrexate	Methotrexate and vincristine	Vincristine	Vincristine and chlorambucil	Procarbazine	Methotrexate, cyclophosphamide, fluorouracil	None
No of patients	19*	1	9	1	1	1	1	2	1

*Includes one patient who received palliative *x*-ray treatment simultaneously.

other agents. Various drug combinations, which include bleomycin, are currently being assessed, especially in the management of the lymphomas, and a second Medical Research Council trial to compare bleomycin and radiotherapy with radiotherapy alone for moderately advanced squamous cell carcinoma of mouth, pharynx, larynx, and oesophagus continues (further participation in this trial would be welcomed).

We thank the many colleagues who have referred patients for treatment. We also thank Professor P B Kunkler for all his help while he served on the working party. Supplies of bleomycin have been made available by courtesy of Lundbeck Research.

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Barbiturate and anticonvulsant treatment in relation to osteomalacia with haemodialysis and renal transplantation

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Summary

Among 39 patients treated by regular haemodialysis for four years or more pathological fractures and histological evidence of osteomalacia were significantly more common in those taking barbiturates. Out of 58 transplant recipients surveyed after one year, seven had osteomalacia; four of these had been taking phenobarbitone and phenytoin and one had taken barbiturates alone. Sedatives and other drugs such as phenobarbitone and phenytoin that induce hepatic microsomal enzymes should probably be avoided when possible in patients with chronic renal failure and after transplantation.

Introduction

Patients on regular haemodialysis at Newcastle upon Tyne have a high incidence of osteomalacia, which is characterised by bone pain, pathological fractures, myopathy, and reduced physical activity.[1 2] Comparison with another British centre confirmed this but showed no obvious differences in dialysis technique.[3] Drug treatment, other than with heparin, vitamin D, calcium supplements, and phosphate binders was not taken into consideration. During the 1960s barbiturates were given regularly at night to patients on dialysis and some of the long-term survivors continued to take them until recently. Prolonged anticonvulsant treatment was given to patients who had convulsions early in the course of their management. Because of the association between anticonvulsants and osteomalacia in epilepsy[4 5] we decided to review the drug treatment of all the patients who had at any time completed not less than four years on regular haemodialysis at Newcastle and to relate it to the incidence of osteomalacia in these patients.

Renal osteodystrophy resolves rapidly after successful renal transplantation.[6 7] The different histological components resolve at different rates, but osteomalacia usually heals promptly. In 81% of our patients with histological evidence of osteomalacia at the time of transplantation the changes had completely resolved a year later.[7] Surprisingly, however, in a few patients with adequate renal function osteomalacia progressed or developed afresh after successful transplantation. Review of these patients showed that many had been treated with anticonvulsants or sedatives for long periods after transplantation.

Patients and methods

Bone histopathology had been studied in serial transiliac bone biopsies. Osteomalacia was diagnosed only when there was an excess of osteoid, with abnormally thick osteoid seams comprising five or more birefringent lamellae, and a reduced or absent calcification front.[8] Radiological skeletal surveys had been carried out at six-monthly intervals. Serum calcium had been measured by atomic absorption spectrophotometry,[9] and all values corrected to a total serum protein level of 72 g/l. Serum alkaline phosphatase had been measured by a modification of the method of Bowers and McComb.[10]

Thirty-nine patients had completed four or more years of regular haemodialysis. Some of them had subsequently been transplanted or died. Complete records of drug treatment were available from their dialysis sheets. Questionnaires on symptoms and records of physical examination had been completed at six-monthly follow-up visits, from which we assessed the degree of bone pain, muscle weakness, and physical activity.

Fifty-eight transplant recipients followed up in the transplant clinic had had a full reassessment of bone status at one year. Their drug treatment was also reviewed. Seven (12%) had had histological evidence of osteomalacia, and of these 5 (71%) had received prolonged treatment with enzyme-inducing drugs. The case histories of these five patients are given below.

CASE 1

A 30-year-old woman received a cadaveric renal transplant on 20 March 1972, three years after beginning regular haemodialysis. After about nine months of regular haemodialysis she had developed symptomatic bone disease, which progressed to pronounced weakness of her quadriceps and difficulty with walking. Osteomalacia was confirmed by transiliac bone biopsy after 14, 27, and 36 months of regular haemodialysis, but no evidence of osteitis fibrosa was found. There was a progressive loss of total and mineralised

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