PRELIMINARY COMMUNICATIONS

Bleomycin in the Reticuloses

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Summary

Bleomycin alone was used in the treatment of 54 patients with Hodgkin's disease in its later stages, 17 with generalized lymphosarcoma, 22 with reticulum cell sarcoma, and 7 with mycosis fungoides. The patients had had radiotherapy and full courses of conventional chemotherapy. Bleomycin was given in doses of 30 mg weekly to an average total dosage of 200 mg, though up to 800 mg could be given because of its marrow-sparing properties. Sixteen (29%) of the patients with Hodgkin's disease remitted, most of them achieving only a partial remission, and similar results were obtained in the other three reticuloses. Bleomycin would seem to have some beneficial action in the late stages of Hodgkin's disease, though it is less effective than some drug regimens recently introduced. Nevertheless it may be useful when there is diminished bone marrow reserve. It would be a suitable drug to use in combination therapy of these four reticuloses.

Introduction

Bleomycin, an antitumour antibiotic derived from *Streptomyces verticillatus*, was discovered by Umezawa (1965) and has been the subject of a number of reports on its effectiveness in a variety of malignant conditions (Ichikawa, 1969; O.E.R.T.C., 1970; K. Kimura, personal communication, 1971). Some response had been reported in the few cases of reticuloses treated, and in view of the low bone marrow toxicity an extended trial in stage III and stage IV Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and mycosis fungoides was undertaken.

Patients and Methods

Of 112 patients treated with bleomycin alone 100 were evaluable. Of these, 54 had Hodgkin's disease, 17 lymphosarcoma, 22 reticulum cell sarcoma, and 7 mycosis fungoides. The diagnoses were based on the histology of lymph node or skin biopsy specimens. The clinical stage of patients with Hodgkin's disease was assessed on conventional criteria, the Rye classification being used (Peters *et al.*, 1966).

Bleomycin was available as a lyophilized powder, each ampoule containing 15 mg of bleomycin. This was made up in saline before intramuscular injection. To most patients it was given in a 15-mg dose twice weekly. To some patients in whom a rapid response was required successive daily doses

of 15 mg were given. The total dosage received by patients ranged from 60 to 810 mg; the average total dose was 200 mg.

Toxic side effects were recorded and, in particular the effect on the peripheral blood count was noted; where relevant, estimations of liver function were done.

Nearly all the patients were in hospital during the early stage of treatment and their subjective and objective responses were noted. They were classified on completion of therapy into complete remission, partial remission, incomplete failure, and total failure of therapy on the criteria used by the European Organization for Research on the Treatment of Cancer (O.E.R.T.C.).

Tolerance

The most common toxic side effect was pyrexia. This followed immediately after intramuscular injection and was seen in 40 patients. Usually the hyperthermic responses became less as the course of treatment progressed. Skin lesions were another common side effect, occurring in 27 patients. They were either oedematous, pigmented, urticarial, hyperpigmented, or scleroderma-like in appearance. Pigmentation of excoriated areas was an unusual feature seen in patients receiving bleomycin (Fig. 1).

Hodgkin's disease; pigmented scratch marks—left upper arm.

The next most common complication was nausea and vomiting in 15 patients and stomatitis in nine. Alopecia was uncommon and no evidence of the severe pulmonary distress reported previously (O.E.R.T.C., 1970) was recorded. The outstanding feature was the lack of bone marrow toxicity—only four patients showed any significant fall in the peripheral blood count. Of these, the platelet count was usually most seriously affected, but thrombocytopenia caused cessation of treatment in only one patient. Toxic side effects—uncontrollable pyrexia, nausea, and vomiting—caused treatment to be stopped in three other patients.

Results

The effect of bleomycin in the 100 evaluable patients is shown in Table I. The low incidence of complete remission is disappointing, but as many as one-third of the patients achieved a partial remission.

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TABLE I—Results of a Trial of Bleomycin in the Reticuloses

Diagnosis	No. of Cases	Complete Remission	Partial Remission	Some Effect	Failure
Hodgkin's disease	54	2	14	16	22
Lymphosarcoma	17	1	6	3	7
Reticulum cell sarcoma ..	22	0	8	4	10
Mycosis fungoides	7	1	3	1	2
Total	100	4	31	24	41

Most of the patients were in a late stage of these diseases and had received a considerable amount of conventional chemotherapy and radiotherapy. This is illustrated by the patients with Hodgkin's disease, half of whom were in stage IVB (Table II).

TABLE II—Patients with Hodgkin's Disease Receiving Bleomycin

No. of cases	Stage: ..	IIB 2	IIIA 2	IIIB 13	IVA 9	IVB 27

Discussion

The combined complete and partial remission rate of nearly 30% in patients with late Hodgkin's disease shows that this agent may be of use in the treatment of this condition. However, the report by Nicholson *et al.* (1970) on combination chemotherapy in late Hodgkin's disease in which patients at a similar stage having had both chemotherapy and radiotherapy achieved a 35% complete remission rate, and the recent report of complete and partial remission in 47% using bis-chlorethyl-nitrosourea (BCNU) (Young *et al.*, 1971), put the present results into perspective. Because of its unique marrow-sparing

property bleomycin should be considered for the treatment of Hodgkin's disease when there is evidence of poor bone marrow reserve.

Of six patients with Hodgkin's disease who had pulmonary infiltration, two showed complete disappearance of infiltration and effusions while in the other four there seemed to be no effect. In two patients with lymphosarcoma, one with an effusion and one with pulmonary infiltration, there was no effect, but a patient with reticulum cell sarcoma and lung metastases responded with complete disappearance of the growth. A feature of the use of bleomycin in reticulum cell sarcoma was the rapid disappearance of skin lesions with small doses, and about half the patients with mycosis fungoides showed a response in the severity and extent of the infiltration. No definite specificity for dermatological lesions was noted and with one exception the dramatic improvements that have been reported in mycosis fungoides were not seen in this series.

Requests for reprints should be addressed to the Secretariat, Co-operative Group, "Leucémies et Hématosarcomes" O.E.R.T.C., Institut de Cancérologie et d'Immunogénétique, Hôpital Paul-Brousse, 14 Avenue Paul Vaillaut Couturier, 94 Villejuif, France.

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MEDICAL MEMORANDA

Fetal Survival after Partial Extrusion into the Bladder

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A case of partial extrusion of the fetus into the bladder is reported. Search of the literature failed to disclose a similar case in which both mother and baby survived.

Case Report

A 38-year-old para 8 gravida 9 was admitted to the labour ward as an emergency case on 22 May 1971. She stated that she was in

her ninth month of pregnancy and that she had been attending one of the district antenatal clinics. Pregnancy had progressed without complication. Labour contractions began seven hours before admission. Three hours previously she started draining blood-stained liquor and developed continuous lower abdominal pain.

Her first seven pregnancies, labours, and puerperia were normal. Her last delivery in 1969 was by lower segment caesarean section for placenta praevia. Notes on that delivery indicated difficulty in obtaining haemostasis because of large veins coursing over the lower segment. The puerperium was uncomplicated.

On admission her general condition was good. The temperature was 98.4°F (36.9°C), pulse 90/min, and blood pressure 110/65 mm Hg. There was some pallor of the mucous membranes. The cardiovascular and respiratory systems were normal. On abdominal examination a median subumbilical scar was present. The uterine fundus was consistent with a 36-week pregnancy. The lie was longitudinal and one-fifth of the head was presenting above the pelvic brim. The lower segment was distended and tender. The uterus was tense between contractions, which lasted 50 seconds every four to five minutes. The fetal heart was audible at 108/min. Vaginal examination showed the cervix to be dilated 4 cm and poorly applied. The vertex was presenting in the occipitoposterior position 2 cm above the level of the ischial spines. Heavily blood-stained liquor drained from the vagina. The urine was blood-stained. Rupture of the previous caesarean scar was diagnosed and immediate resuscitative measures were begun. One litre of compatible blood was ordered and the patient was transferred to the theatre.

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