CLINICAL TRIALS OF *p*-(DI-2-CHLOROETHYLAMINO)- PHENYLBUTYRIC ACID (CB 1348) IN MALIGNANT LYMPHOMA

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Everett, Roberts, and Ross (1953) synthesized a series of water-soluble aromatic nitrogen mustards, one of which, *p*-(di-2-chloroethylamino)-phenylbutyric acid (CB 1348), was found to be a powerful inhibitor of the transplanted Walker rat tumour 256 (Haddow, 1952) and was submitted for clinical trial.

Ninety-three patients suffering from advanced carcinoma and from lymphomas have been treated with CB 1348 since September, 1952. This report concerns only the cases of malignant lymphoma, of which there were 76. Fourteen of these have been omitted from the report because the diagnosis was in doubt, because of inadequate follow-up, or because incomplete treatment was given. The 62 remaining cases include 23 of Hodgkin's disease, 20 of lymphocytic lymphoma (including eight cases of chronic lymphocytic leukaemia), 11 of reticulum-cell sarcoma, 6 of follicular lymphoma, and 1 each of generalized exfoliative erythrodermia and mycosis fungoides.

Administration, Dosage, and Side-effects

Administration was usually by mouth, but a few patients received the sodium salt intravenously, either alone or in addition to oral therapy. The sodium salt was given intraperitoneally to one patient with disseminated reticulum-cell sarcoma and ascites.

With few exceptions the oral dose ranged from 2 to 20 mg. a day (0.03–0.34 mg. per kg. of body weight). In most cases it was either 0.1 or 0.2 mg. per kg. daily (6 or 12 mg. for a patient weighing approximately 10 stone—63.5 kg.). A course of treatment usually lasted three to six weeks, but CB 1348 was given daily for 8 to 16 weeks on thirteen occasions and for 6 to 12 months on three. Eighteen patients had more than one course of treatment; 15 were given two courses at intervals of from 3 to 27 months; two had three courses; and one (Case 4) had six.

Treatment with CB 1348 was stopped when satisfactory improvement had been obtained. In some cases a course had to be terminated because of neutropenia or thrombocytopenia. If there was no response treatment was usually continued for six weeks before concluding that the patient was resistant to the drug. Prolonged treatment was given when improvement was pro-

gressive and the blood picture offered no contraindication. Twenty-five patients received more than 0.5 g. of CB 1348, the largest total dose being in Case M. W. (Table III), who was given 1.93 g. in the course of 12 months' continuous treatment.

Four patients complained of epigastric or retrosternal burning pain, and a patient with a duodenal ulcer developed recurrence of dyspeptic symptoms after taking 6 mg. of CB 1348 daily for one month. This patient later took the drug for two months without ill effect.

Four patients with Hodgkin's disease were given three- or four-day courses to a total dose of 120 mg. (1.65–2 mg. per kg.). All experienced nausea and two vomited once. This method of treatment has no advantage and has been discontinued.

For intravenous use, the sodium salt was freshly made up in isotonic sodium bicarbonate. Single doses varied from 10 to 20 mg. In one case single doses of 70 mg. were given. The injections were always well tolerated, and did not damage the veins or cause vomiting. However, doses of 100 mg. were given in some cases of advanced carcinoma not included in this report, and were usually followed 6–18 hours later by vomiting. Intraperitoneal injection was well tolerated.

Results

The results are summarized in Table I. By "benefit" we mean improvement of real value to the patient, so that as a result of treatment he can return to something approaching a normal life for at least six months. Improvement of shorter duration, however striking, is classed only as "some effect."

TABLE I.—Results of Treatment with CB 1348 in 62 Cases of Lymphoma

Diagnosis	No. of Patients	Benefit	Some Effect	No Effect
Hodgkin's disease	23	4	14	5
Reticulum-cell sarcoma	11	0	6	5
Lymphocytic lymphoma, subleukaemic	12	7	3	2
Chronic lymphocytic leukaemia	8	4	1	3
Follicular lymphoma	6	5	1	0
Mycosis fungoides	1	0	0	1
Exfoliative erythrodermia	1	0	1	0
Total	62	20	26	16

Hodgkin's Disease

Twenty-one patients had been ill for six months to six years and had already received specific treatment. Most of them had had deep x-ray therapy and a few had had di-(2-chloroethyl)-methylamine (HN₂, mustine), di-2-chloroethyl-β-naphthylamine (CB 1048, formerly R 48), or triethylene melamine (T.E.M.). Two had not been treated previously. One had generalized disease of acute onset. In the other the disease was apparently confined to a single mass of mediastinal nodes.

Four patients derived real benefit (Cases 1–4). Fourteen responded in some degree, showing favourable effects on fever, sweats, pruritus, enlarged lymph nodes, spleen, and haemoglobin level. However, these effects were short-lived and of little clinical importance. In five patients CB 1348 failed to influence the condition at all.

Case 1.—A woman of 63 was admitted with generalized Hodgkin's disease of acute onset in April, 1953. She was given CB 1348, 10 mg. daily (0.2 mg. per kg.) for 38 days. Within the first 14 days of receiving the drug, fever and sweats abated, skin rash faded, pruritus was relieved. Rapid regression of enlarged ulcerated tonsils, cervical, axillary, and inguinal nodes, and spleen followed. The Hb level rose

by 33% (4.9 g. per 100 ml.), reaching 108% (16 g. per 100 ml.) in six months. The spleen began to enlarge 15 months after treatment was stopped, but the patient remained well for another two months. Her condition then deteriorated; the Hb level fell 20% (2.96 g. per 100 ml.), the platelet count dropped from above 200,000 to below 100,000 per c.mm., and the neutrophil count fell from 11,000 to 3,100 per c.mm. In spite of this a second course of CB 1348, 10 mg. daily for 22 days, was given in January, 1955. She remained weak and febrile, and the fall in haemoglobin level and enlargement of lymph nodes, liver, and spleen continued. No further neutropenia or thrombocytopenia ensued and treatment was abandoned because it was ineffective. Cortisone was given without benefit. She died on February 28.

Case 2.—A boy of 14 was found to have enlargement of cervical and axillary nodes and splenomegaly in December, 1952. A diagnosis of Hodgkin's disease was made by biopsy of a lymph node. Radiotherapy caused the nodes and spleen to regress, but one month later he experienced the first cycle of severe remittent fever. Treatment with CB 1348 was begun in May, 1953, with doses of 6–10 mg. daily (maximum 0.2 mg. per kg.) for seven weeks (total 420 mg.). The febrile attacks were favourably modified; he gained weight and was able to return to school for six months. In February, 1954, the febrile attacks again became severe. Further treatment with CB 1348 was effective for only a few weeks; the fever became continuous and he died in August, 1954.

Case 3.—A man of 33 had had Hodgkin's disease for five years, for which he had been given radiotherapy and T.E.M. In January, 1954, he was febrile, anaemic, anorectic, and had lost weight. He was given CB 1348, 10 mg. daily for 14 days (0.13 mg. per kg.). Fever abated, he gained 43 lb. (19.5 kg.) in weight, the enlarged liver and spleen regressed, and the Hb level rose 39% (5.8 g. per 100 ml.). The remission lasted almost a year, a previous remission after treatment with T.E.M. having lasted only three months. A second course of CB 1348, 10 mg. daily for three weeks, was given in December, 1954, because of recurrence of sweating, fever, anorexia, and loss of weight. The response, though satisfactory, was short-lived, and a third course at the same dosage was given in April, 1955, again with relief of symptoms. In October, 1955, he was free from symptoms.

Case 4.—A woman of 44 had had Hodgkin's disease for six years. She had been treated with deep x-ray therapy and T.E.M. In December, 1953, she had fever, anorexia, and hepatosplenomegaly. Since then she has had six courses of CB 1348, 10 mg. daily (0.18 mg. per kg.)—for three weeks in the first two courses, for five to seven weeks in the last four. Each time fever subsided, weight increased, and the spleen regressed. The remission after the first course lasted four months; that after the sixth lasted 6 weeks. The response to CB 1348 was better than to T.E.M.

The results of treatment in generalized Hodgkin's disease are disappointing, because so few patients secured worthwhile benefit. In these few patients the results were striking, but we cannot recognize any special feature common to the successfully treated patients that distinguishes them from the larger number who responded less well or not at all. In eight cases comparison can be made between the efficacy of CB 1348 and that of previous and subsequent chemotherapy. In two cases CB 1348 gave a better response than T.E.M.; in two T.E.M. seemed better, but in one of these CB 1348 was given late in the disease. In one case the response to CB 1348 was similar to that previously obtained with R 48 (CB 1048), mustine, and T.E.M. In another, CB 1348 and T.E.M. were equally ineffective, but a good response was obtained to radiotherapy. In one case the temporary response to actinomycin C was similar to that previously obtained with CB 1348. In another case the response to a combination of CB 1348 and cortisone was better than to either alone. Later a course of T.E.M. and cortisone had a similar effect.

Lymphocytic Lymphoma

1. Chronic Lymphocytic Leukaemia

All eight patients had enlarged spleens and livers. Only two had received previous treatment other than blood transfusions. Anaemia was severe in five cases (Hb level below 45%—6.3 g. per 100 ml.) and moderate in three (Hb level 67% to 79%—10 to 11.7 g. per 100 ml.). The results are summarized in Table II.

In four of the five severely anaemic patients frank haemolysis was demonstrated. Response to treatment with CB 1348 was good in one of these (Case 5) and in the severely anaemic patient without evidence of haemolysis (Case 6). The three remaining patients with evidence of haemolysis did not respond to CB 1348. In two the direct antiglobulin test was positive, and one of these patients responded temporarily to cortisone.

Case 5.—A woman of 77 was found to have chronic lymphocytic leukaemia. The spleen was grossly enlarged. A transfusion of 3 pints (1.7 litres) of blood did not raise the haemoglobin level or prevent its fall. The direct antiglobulin test was negative. The bone marrow showed considerable erythropoietic activity and many of the lymphocytes in the blood were early forms. In August, 1953, she was given CB 1348, 6 mg. daily (0.1 mg. per kg.) for 23 days (total 138 mg.), followed 11 days later by a further 70 mg. in 14 days. During treatment a transfusion of 4 pints (2.3 litres) of blood raised the haemoglobin level from 39% to 54% (5.8 to 8 g. per 100 ml.) and a further rise to 82% (12.2 g. per 100 ml.) followed in the next 10 weeks. The spleen regressed, the leucocyte count fell to normal, although relative lymphocytosis persisted, and the platelet count rose from 90,000 per c.mm. before treatment to 300,000 three months later. Three short courses of 2 mg. of CB 1348 daily lasting two to four weeks were given during the next four months. She remained well for one year, but subsequently failed to respond to CB 1348, to irradiation of the spleen, or to cortisone.

Case 6.—A man of 76, with no demonstrable haemolysis, obtained a good response after treatment with CB 1348, 6 mg. daily (0.1 mg. per kg.) for 20 days. The platelet count remained below 100,000 per c.mm. for seven weeks, but subsequently rose above this level. The Hb rose from 42 to 84% (6.2 to 12.4 g. per 100 ml.) in three months. Eleven months later he had relapsed.

Two of the three moderately anaemic patients, none of whom had received previous treatment, responded well to CB 1348. One was thrombocytopenic before treatment. The third had few symptoms and his condition was substantially unchanged by treatment (W. F. Table II).

Case 7.—A woman of 54 bruised easily and was found to have moderate enlargement of the liver and spleen, a positive capillary fragility test, and a platelet count of 45,000 per c.mm. She was given CB 1348, 10 mg. daily (0.2 mg. per kg.) for 27 days (total 5.4 mg. per kg.). The spleen regressed for four months after the treatment, but remained just palpable. The liver became impalpable. The Hb level rose 15% (2.22 g. per 100 ml.) in six months. The platelet count fell during treatment and for two weeks afterwards, but rose quickly thereafter. It remained between 100,000 and 200,000 per c.mm. for 16 months. Two months later the platelet count was 35,000 per c.mm. but again rose after treatment with cortisone and CB 1348. She is well 2½ years from the time of diagnosis.

In the following case, CB 1348 was given continuously over a period of seven months.

Case 8.—A man of 62 was found to have chronic lymphocytic leukaemia during investigations for bronchiectasis. During seven months of treatment with CB 1348 (4–10 mg. daily—0.05–0.14 mg. per kg.; total 1.3 g. in 28 weeks) regression of lymph nodes, spleen, and liver took place, he gained 20 lb. (9 kg.) in weight, and the Hb level rose 20%. The leucocyte count fell from 160,000 to 14,000

TABLE II.—Eight Patients with Lymphocytic Leukaemia. Results of Treatment with CB 1348

Case No.	Sex	Age	Condition Before Treatment					Dose of CB 1348				Condition After Treatment			Remarks
			Hb* %	Direct Anti-globulin Test	Evidence of Haemolysis	Platelets per c.mm.	Splenic Enlargement	Max. (mg./day)	Max. (mg./kg. per day)	Duration (Weeks)	Total (mg.)	Effect on Spleen	Effect on Hb %	Effect on Platelets (per c.mm.)	
5	F	77	37	—	+	90,000	Gross	6 2	0.1 0.03	6 11	208 126	Moderate regression	Reached 82% in 10 weeks	100,000–300,000 in 10 counts during 1 year	Good remission 1 year. No subsequent response to CB 1348 or cortisone
6	M	76	42	—	—	56,000–90,000	„	6	0.1	3	120	Marked regression	Reached 84% in 17 weeks	90,000–150,000 in 7 counts during 4 months	Good remission 1 year
R. E.	F	71	40	+	+	70,000	Moderate	4	0.1	16	112	Moderate regression	Reached 68% in 10 weeks	Nil	Temporary response to cortisone given concurrently with CB 1348. Fatal haemolytic crisis
W. G.	M	70	39	+	+	320,000	Slight	8	0.12	12	566	Nil	Nil	„	Cortisone and splenectomy also without effect
M. G.	M	64	40	—	+	180,000	Gross	6	0.1	6	214	„	„	Fell to 58,000	No benefit
7	F	54	79	—	—	45,000	Moderate	10	0.2	4	270	Marked regression	Reached 94% in 6 months	Fell to 12,000; subsequent rise to 200,000	Remission maintained 18 months; then recurrence of thrombocytopenia
8	M	62	67	—	—	450,000	„	10	0.14	28	1,314	„ „	Reached 87% in 6 months	Fell to 250,000	Remission in progress 11 months
W. F.	M	59	72	—	—	70,000	Gross	6	0.1	6	162	Slight regression	Nil	Nil	Unchanged. Stationary 13 months later

* 100% Hb = 14.8 g. per 100 ml.

TABLE III.—Twelve Patients with Lymphocytic Lymphoma. Results of Treatment with CB 1348

Case	Sex	Age	Dose of CB 1348			Duration of Treatment (Weeks)	Clinical State Before Treatment	First Evidence of Benefit Weeks After First Dose	Maximal Improvement Attained. Weeks After First Dose	Duration of Improvement from Start of Treatment (Months)	Comments
			Daily (mg.)	Max. Daily (mg./kg.)	Total (mg.)						
H. M.	F	30	6–10	0.17	418	12	Incapacitated. Hb 82%	3	11	27 Continues	Resumed household duties. Spleen and liver became impalpable. Nodes regressed. Hb rose 20%
T. F.	M	58	6–20	0.3	792	12	Incapacitated by abdominal pain. Not anaemic	2	12	20 Continues	Pain associated with abdominal nodes improved after 2 weeks. Complete regression nodes all areas. Recurrence one node 1 year later. No further treatment. Working
M. W.	M	64	2–6	0.1	1,930	52	Seriously ill. Hb 85%	4	36	12	Further radiotherapy precluded by skin condition. Resumed work 3 months after treatment. Liver and spleen impalpable after 9 weeks. Nodes continued to regress for 9 months. Recurrence 14 months. Died septicaemia 15 months
S. W.	M	57	2–10	0.15	596	15	Incapacitated. Hb 63%	3	6–10	7 Continues	Much previous radiotherapy. Resumed work 6 weeks after first dose. Three months later spleen, liver, nodes had regressed completely. Hb rose 30%
R. W.	M	61	10	0.15	540	8	Seriously ill. Not anaemic	2	12	5 Continues	Radiotherapy only locally helpful. Regression of nodes, skin plaques, oedema, and improvement in pleural effusion followed CB 1348. Fit to resume work
P. R.	F	44	6–10	0.15	350	5	Incapacitated. Not anaemic	2	5	4 Continues	Complete regression of spleen and nodes. Resumed household duties
I. W.	M	70	6–10	0.13	440	8	Seriously ill. Hb 50%	3	8	4 Continues	Resumed work 2 months after first dose. Regression of liver, spleen, nodes, oedema. Spleen enlarging 4 months.
S. V.	M	68	12	0.16	240	3	Seriously ill. Purpuric. Hb. 40%	1	2	0.5	Exacerbation of purpura precluded further treatment. Died 3 months later
H. W.	F	64	6	0.09	168	4	Good. Complained of enlarged nodes only	2	4	1	Improvement only slight and not maintained. Treatment discontinued on account of leucopenia. Subsequent temporary improvement after ³² P, which also induced leucopenia and purpura
P. P.	M	67	10	0.13	330	4	Fair. Neutrophil count 1,000 per c.mm. Hb. 66%	3	?	?	Neutropenia worse after CB 1348. Cellulitis from small septic focus responded to antibiotics. No follow-up
W. M.	F	67	4	0.1	190	7	Seriously ill. Hb 70%	Nil	Nil	Nil	No previous treatment. Disease present 3 years. Failed to respond to subsequent radiotherapy. Died 2 months after start of treatment
C. M.	F	70	10	0.14	212	4	Seriously ill. Hb 75%	„	„	„	Responded 6 months previously to radiotherapy. Died 4 weeks after start of treatment

per c.mm. but the differential count remained abnormal throughout. His major disability has been associated with the chronic lung condition and he has required no further treatment for his leukaemia for four months after completing the first course.

2. Lymphocytic Lymphoma without Leukaemia

These 12 patients were closely similar to those with overt lymphocytic leukaemia. All had generalized lymph-node enlargement; some had enlargement of the liver and spleen; in all of five cases in which the bone marrow was examined heavy lymphocytic infiltration was present, but the peripheral leucocyte counts were normal or showed only moderate lymphocytosis. Seven patients had already had deep x-ray therapy. Before receiving treatment with CB 1348, 10 of the patients were incapacitated, six being seriously ill. Seven of these incapacitated patients, including three of those seriously ill, derived benefit from CB 1348. They have remained well and able to work for periods up to 27 months. Two of the remaining five patients responded for short periods only. The other three obtained no benefit. The results are summarized in Table III.

Thus 11 of the 20 patients with lymphocytic lymphoma, with and without leukaemia, obtained significant clinical benefit from CB 1348 treatment. In three cases radiotherapy had ceased to be effective, while in three treatment was successful in the presence of platelet counts between 45,000 and 100,000 per c.mm.

Follicular Lymphoma

All six patients had generalized lymph-node enlargement, five had splenomegaly and three had constitutional symptoms; three had at some stage moderate peripheral lymphocytosis, in one case up to 50,000 lymphocytes per c.mm. The daily dosage was 0.1–0.2 mg. per kg. Three patients were treated for four to seven weeks and three for 10 to 16 weeks. The total dosage was from 168 to 504 mg. Five patients derived benefit; symptoms were relieved and almost complete regression of spleen and nodes took place. Improvement started within three weeks of the beginning of treatment and progressed over the next few weeks. Four patients were moderately anaemic when treatment began, and in three of them the haemoglobin rose to the normal level. In the sixth case very small doses of CB 1348 were given because the patient was in a terminal neutropenic state and only short-lived benefit resulted.

One patient has remained free of recurrence for 20 months without further treatment. One has a few palpable lymph nodes after 16 months. In another, recurrences appeared after a year, but further treatment was postponed until symptoms returned two years after the initial treatment was completed. A good response was obtained to a second course of CB 1348 (0.05 to 0.1 mg. per kg. for 56 days) in this patient and in another who developed generalized recurrence 2½ years after the first course (0.1 mg. per kg. for 28 days).

CB 1348 has been as effective in follicular lymphoma as any other treatment; it is more convenient than radiotherapy, less disturbing to the patient than mustine, and safer than T.E.M.

Reticulum-cell Sarcoma

These 11 patients had rapidly progressive disseminated disease that had begun as locally invasive focal lesions except in one case in which multiple metastases were present when medical advice was sought. In three cases the histological picture, though pleomorphic and essentially undifferentiated, showed some lymphoid maturation. Seven patients had previously been treated with radiotherapy or radioactive phosphorus.

Treatment with CB 1348 led to some improvement in six cases. In three the effects of treatment were striking, but improvement was not maintained longer than three months and there was no response to subsequent courses. In a

cachectic patient with extensive skin involvement complete regression of lesions with healing of secondarily infected ulcers followed treatment with large intravenous doses of CB 1348, but agranulocytosis and thrombocytopenia ensued.

Exfoliative Erythrodermia

Remarkable but short-lived improvement took place in the patient with exfoliative erythrodermia, radioactive phosphorus having been ineffective. Similar transient improvement was later observed after treatment with radioactive arsenic.

Toxic Effects on Blood Elements

Lymphocytes.—Many patients showed lymphopenia during treatment, usually slowly progressive, though irregularly so and continuing as long as the drug was given. Sometimes lymphocytes disappeared from the blood. After treatment normal levels were usually rapidly regained.

Neutrophils.—Most patients showed some neutropenia after the third week of treatment. Falls of 20–60% from pretreatment neutrophil counts were common and recovery was rapid. In one case the neutrophil count continued to fall for 28 days after treatment was stopped, but in no other instances did neutropenia continue for more than 10 days after the last dose. Eleven patients developed more severe neutropenia, but two had 1,000 neutrophils per c.mm. or less before treatment. In the others the neutrophil count fell to 1,000 per c.mm. or less, representing a fall 85–95% below pretreatment levels. Five patients recovered rapidly; the others were all in the terminal stage of their disease and at the time of death were still neutropenic. This severe neutropenia was closely related to the dosage of CB 1348 (Table IV), for all but one patient received a total dose of

TABLE IV.—Incidence of Severe Neutropenia* in 60 Patients† Treated with CB 1348. Relation to Dosage

	No. of Patients	Total Dose of CB 1348			
		500 mg. or More	Less than 500 mg.	6.5 mg. per kg. Body Weight or More	Less than 6.5 mg. per kg. Body Weight
Developing severe neutropenia ..	9	6 (4)	3	8 (5)	1
Not developing severe neutropenia ..	51	18 (9)	33	22 (11)	29
Total ..	60	24 (13)	36	30 (16)	30

* Severe neutropenia is recorded when neutrophil count is 1,000 per c.mm. or less.

† Two patients with severe neutropenia before treatment are omitted.

Figures in parentheses represent numbers of patients who received total dose in 8 weeks or less.

6.5 mg. per kg. or more (450–550 mg.) in one course. The remaining patient received 5.7 mg. per kg. in eight weeks. About a quarter of all patients receiving 6.5 mg. per kg. may be expected to develop severe neutropenia, and if this dose is taken in eight weeks or less the proportion approaches one-third. It may be significant that 16 of the 20 patients who derived most benefit from treatment received comparatively small doses, and this suggests that administration of CB 1348 need not be pushed to its limits of tolerance to achieve the best therapeutic results.

Patients with carcinomatosis tolerate larger doses with less risk of haematological depression. One patient with advanced carcinoma of the rectum was given 2.23 g. (32 mg. per kg.) in eight months without any effect on the blood picture. However, a patient with extensive skeletal metastases from anaplastic carcinoma of the fundus uteri who received only 120 mg. of CB 1348 in three days (approximately 3 mg. per kg.) suffered a 75% depression of neutrophils, to fewer than 1,000 per c.mm. The platelet count fell to 60,000 per c.mm. In the lymphoma group most patients who developed severe neutropenia and thrombocytopenia had infiltration of the bone marrow, but others who tolerated the drug well had similar infiltration.

Platelets.—Platelet depression was rarely serious in patients treated with CB 1348. In 11 cases treatment was given although the platelet count was below 100,000 per c.mm. Five were cases of chronic lymphocytic leukaemia and in three treatment led to a sustained rise in the platelet count to above 100,000 per c.mm. (Cases 5, 6, and 7). In Case 7 this rise was preceded by a brief purpuric phase during which the platelet count was further depressed. These were three of the patients who responded best to CB 1348. The platelet count was unaffected in the fourth case and continued to fall in the fifth. In two of the remaining six patients given CB 1348 despite pre-existing thrombocytopenia there was further depression of the platelet count.

Discussion

The disadvantages of existing methods of treatment of the lymphomas are well known. A preparation of similar efficacy but lacking the side-effects and toxic properties of existing cytotoxic drugs would find a place in therapeutics. To some extent CB 1348 fulfils these requirements. It is relatively free from side-effects: from our limited experience it is at least as effective as any other method in follicular lymphoma and in lymphocytic lymphoma. In the latter group particularly, treatment by conventional agents is often unsuccessful because dosage is limited by thrombocytopenia, or in the subleukaemic group by low leucocyte counts; yet CB 1348 has been used successfully in these circumstances. In Hodgkin's disease the proportion of patients who responded well is small; but useful remissions have been obtained, in two instances better than those following T.E.M. CB 1348 is safer than T.E.M.: this is especially important when repeated courses are required, for it is rarely safe to give more than three courses of T.E.M. Unexpected and irreversible bone-marrow damage following previously well-tolerated doses of T.E.M. is not uncommon even when the blood picture is apparently normal before treatment (Haddow, 1953; Nabarro, 1953). With CB 1348 up to six courses have been given safely. Severe bone-marrow damage can follow CB 1348 administration, but it is usually the result either of excessive dosage or of treating patients with impaired bone-marrow function.

The dosage likely to cause bone-marrow damage almost always lies well outside the therapeutic range, at any rate for first courses. For these reasons we believe CB 1348 deserves further trial in the treatment of malignant lymphoma.

Suggestions for the Routine Use of CB 1348

CB 1348 may be safely used in routine therapy if simple precautions are taken to avoid damaging the bone marrow. The marrow is especially vulnerable (1) shortly after a course of treatment with ionizing radiations or cytotoxic drugs, including CB 1348 itself; (2) when it is infiltrated with lymphomatous tissue; and (3) when it is hypoplastic as a result of long-standing and usually extensively treated disease. CB 1348 should therefore not be used within four weeks of the end of a full course of radiation therapy or chemotherapy.

When small doses of palliative x-radiation have been given over small fields remote from foci of bone marrow, the neutrophil and platelet counts will not usually be depressed and chemotherapy may be safely started. If one or both of these counts are depressed, treatment should be postponed until normal counts are obtained, usually one or two weeks later. Whether treatment has been given or not, persistently low neutrophil and platelet counts or peripheral lymphocytosis should lead to suspicion of bone-marrow infiltration. Marrow puncture should be performed in these cases. If lymphocytic infiltration is present, as is frequently the case in lymphocytic lymphoma and sometimes in follicular lymphoma, CB 1348 may be given, but at less than standard dosage. In some cases of Hodgkin's disease when marrow cannot be obtained from several sites by aspiration, trephine specimens may show extensive fibrosis. These cases are not suitable for chemotherapy.

The standard daily dose is 0.2 mg. per kg.; the whole dose is given at once and no special precautions are necessary. When lymphocytic infiltration of the bone marrow is present, or when the marrow is hypoplastic, the daily dose should not exceed 0.1 mg. per kg. Out-patient supervision is satisfactory in the less seriously ill patients, but during treatment approximately weekly visits are essential so that haemoglobin estimation and total and differential leucocyte counts can be performed; routine platelet counts may be omitted provided skin and mucous membranes are inspected for haemorrhagic phenomena. It is not safe to leave a patient for more than two weeks without clinical and haematological examination, and it is helpful to plot the blood counts at each attendance on a chart on which temperature, weight, and spleen size may also be recorded.

Clinical improvement is usually evident in the third week of treatment, but a four-weeks trial is necessary before giving up treatment as ineffective. Administration need not be discontinued as soon as the neutrophil count begins to fall, but it should be remembered that the fall may continue for 10 days after the last dose, and that as the total dose approaches 6.5 mg. per kg. there is a real risk of causing irreversible bone-marrow damage. An average course at 0.2 mg. per kg. per day might last four weeks (5.6 mg. per kg.). If maintenance therapy is contemplated in patients who show slowly progressive improvement during the initial weeks of treatment, who tolerate the drug well, and whose blood picture remains stable, the maintenance dose should not exceed 0.1 mg. per kg. per day, and may well be kept at 0.03 mg. per kg. It is probable that short courses of treatment carry less risk than maintenance therapy. Both methods have been effective; but it is possible that continuous therapy may give an illusion of "maintenance" to a remission that would have proceeded without further treatment.

Summary

Sixty-two patients suffering from malignant lymphoma have been treated with *p*-(di-2-chloroethylamino)-phenylbutyric acid (CB 1348), a water-soluble aromatic nitrogen mustard. There were 23 patients with Hodgkin's disease, 11 with reticulum-cell sarcoma, 12 with lymphocytic lymphoma, 8 with chronic lymphocytic leukaemia, 6 with follicular lymphoma, 1 with mycosis fungoides, and 1 with exfoliative erythrodermia.

Striking remissions were obtained in four cases of Hodgkin's disease, seven of lymphocytic lymphoma, four of chronic lymphocytic leukaemia, and five of follicular lymphoma.

CB 1348 therapy is relatively free from gastrointestinal side-effects and has proved to be less damaging to haemopoietic tissue than cytotoxic agents hitherto available for the treatment of malignant lymphoma.

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