CYCLOPHOSPHAMIDE

(Endoxana)

An Account based on the Proceedings of a Symposium held at the Royal College of Surgeons of England on 4 October, 1963, sponsored by Ward, Blenkinsop & Co., Ltd.

Edited by

G. Hamilton Fairley and J. M. Simister

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CHAIRMAN: VICTOR RIDDELL, M.D., F.R.C.S.
St. George's Hospital, London

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Cyclophosphamide is the B.P. Approved Name and International Approved Name for 2-[di(2-chloroethyl)amino]-1-oxa-3-aza-2-phosphacyclohexane 2-oxide

Alternative chemical names are:—

N,*N*-bis-(β-chloroethyl)-*N'*orthopropylenephosphoric acid ester diamide

2H-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl) amino] tetrahydro-, 2-oxide, hydrate

The drug has trade names in different countries as follows:—

Cytoxan	(U.S.A.)
Endoxan	(Germany and all countries not specified in this list)
ENDOXANA	(U.K.; Irish Republic; Ceylon)
Enduxan	(Brazil)
Genoxal	(Spain)
Procytox	(Canada)
Sendoxan	(Sweden)

And formerly had code names as follows:—

B 518	Germany
NSC-26271	(U.S.A.)

PREFACE

THIS book is based on a symposium on cyclophosphamide held at the Royal College of Surgeons of England on 4 Oct., 1963. The arrangement of the book corresponds with the division of the day's proceedings into sessions devoted to malignant disease of lymphoreticular tissue, other malignant tumours, and suppression of cellular immunity. Some of the papers read are published here in abridged form, and some of the illustrations have been omitted. We have included a few accounts and reports that lack of time or absence of the author prevented us from hearing at the symposium. In some instances we have rearranged contributions from individual authors so that the subject matter fits into the whole more logically.

The result will, we hope, be of value to all who are interested in cancer chemotherapy both in this country and abroad. We hope, too, that the addition of a cyclophosphamide bibliography and the inclusion of references in the index will enable readers to look further into aspects of the use of the drug not adequately covered in the text. References to published work not specifically relating to cyclophosphamide appear as footnotes on the relevant page of text.

Many people were concerned in the arrangement and smooth conduct of the symposium and in the production of this book. We are enormously grateful to Mr. Victor Riddell, who as chairman was no mere figurehead but an active and constructive mentor throughout the preparatory weeks, and the acme of diplomacy, dignity, and authority on the day. We thank Sir Ronald Bodley Scott for undertaking the difficult duties of chairman of the panel and for ending the proceedings on a humorous note. We are grateful to all those who participated in the proceedings of the symposium and who contributed material for this book. We thank Sir Russell Brock and the Council for the hospitality of the Royal College, and Mr. William Davis and the College officials for the admirable organization of the lecture-room facilities and of the refreshments. Mrs. Violet Findlay and Miss Ruth Graff did all the secretarial work before and after the symposium, and did it splendidly.

The shorter the interval between such a symposium and the publication of its proceedings the greater the value of the book. That there has been an eight-month wait in this case has been no fault of the publishers, whose competence, artistry, and patience have been beyond reproach. Our special thanks are due to Mr. L. G. Owens for his helpful co-operation and quiet efficiency.

We acknowledge with thanks the generosity of Ward, Blenkinsop & Co. Ltd., the sponsors of the symposium and of this book.

June, 1964

G. H. F.
J. M. S.

LIST OF PARTICIPANTS AND AUTHOR INDEX

FOREWORD

ALTHOUGH over eight hundred papers relating to cyclophosphamide have been published in the world's literature since Arnold and his colleagues announced the synthesis of the compound in 1958, the true clinical value of the drug is still not precisely known. Of the thousands of compounds tested as potential anti-tumour drugs only a handful have so far shown themselves to be worthy of a place in the treatment of cancer in man. Among these must be counted cyclophosphamide.

By 1963 cyclophosphamide had been in clinical use in Britain for four years, and it was felt that a meeting here of clinicians to discuss its use in the treatment of malignant disease might lead to greater precision in the selection of appropriate cases, and in the choice of dosage and route of administration.

Recently there has been a great deal of interest throughout the world in the homotransplantation of tissues and organs. Homografting in man of the lung, the liver, and the spleen have been reported, and some two hundred patients have received homograft kidneys. One of the major problems in organ transplantation is the prevention of rejection of the foreign graft. Cellular immunity has been suppressed by radiotherapy and more recently by chemotherapy. The role of cyclophosphamide in this field and in the related one of 'auto-immune disease' was thought worthy of preliminary discussion.

Accordingly a one-day symposium devoted to cyclophosphamide was arranged, and held at the Royal College of Surgeons of England on 4 Oct., 1963. At this symposium physicians and surgeons from England, Scotland, and Ireland and abroad described aspects of their experience with the drug in particular forms of malignant disease, and discussed problems of dosage, administration, and side-effects in relation to therapeutic success or failure. Malignant disease of lymphoreticular tissue was the subject of the first part of the symposium; the second and longest session concerned other malignant tumours, considered according to anatomical site; the third session was devoted to the effect of the drug in suppressing cellular immunity, and included accounts of human kidney and dog lung homografting, of experimental animal work relating to allergy and hypersensitivity, and of preliminary clinical work relating to auto-immune disease. The day ended with a Panel Discussion under the chairmanship of Sir Ronald Bodley Scott.

This book is a record of the papers contributed to the symposium. Though most of these were read and discussed at the meeting, some were not read, either because of shortage of time or because the author was unable to attend.

The place of cyclophosphamide in chemotherapy is clearer now. Its clinical use is a step towards more specific attack on malignant tissue and more specific suppression of cellular immunity. In these fields it is the drug of today. The drug of tomorrow will be a keener rapier wielded by a better swordsman. The co-operation between Academic Medicine and the Pharmaceutical Industry will surely produce a better understanding of cell growth and its control, and the day will come when cancer can be cured by chemotherapy, and when damaged tissues and organs can be permanently replaced by healthy grafts.

VICTOR RIDDELL

St. George's Hospital,
*London, S.W.*1
March, 1964

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(Endoxana)

PART I. RETICULOSES
(MALIGNANT DISEASES OF LYMPHORETICULAR TISSUE)

HODGKIN'S DISEASE

DR. G. HAMILTON FAIRLEY (*St. Bartholomew's Hospital, London*)

OF all malignant diseases, those arising in lymphoreticular tissue (reticuloses) respond most consistently and often dramatically to nitrogen mustards, and Hodgkin's disease is no exception. During the past fifteen years a large number of patients under the care of Sir Ronald Bodley Scott, at St. Bartholomew's Hospital, have been treated with various forms of nitrogen mustard, including cyclophosphamide, and we felt it might be of value to discuss the results of treatment with this drug, to review the indications for its use, and to compare it with other nitrogen mustards.

Results of Treatment with Cyclophosphamide

Sixty-two patients with Hodgkin's disease have been treated with cyclophosphamide for a variable period up to three years. Of these, 54 had previously received some other form of treatment, i.e., radiotherapy, mustine hydrochloride, chlorambucil, or corticosteroids, and in only 8 was cyclophosphamide the first form of treatment used. Twenty-nine patients are still alive and 33 are dead. Because of the difficulties in assessing the efficacy of any form of treatment in a disease like Hodgkin's disease with such a variable course, only the initial results of treatment will be presented, and for the purpose of analysis all the patients will be considered as one group, whether they have previously been treated with other agents or not.

The overall results are shown in *Table I.* Cyclophosphamide was beneficial, i.e., it produced subjective or objective improvement, in 43 patients (69 per cent), 6 patients (10 per cent) were unaffected, and in 13 patients (21 per cent) the treatment failed. In these 13 treatment failures there was clinical deterioration in 9 while the patients were receiving the drug, and the treatment was abandoned in 4 because of nausea and vomiting in 2, profound leucopenia in 1, and refusal to take tablets in another.

Table II shows the effect of cyclophosphamide on various symptoms and signs in 58 patients with Hodgkin's disease (the 4 in whom treatment was abandoned having been omitted). Subjective improvement was assessed by the symptoms of malaise, pruritus, and pain when this could definitely be attributed to the disease. Twenty-nine patients complained of malaise; 20 (approximately 70 per cent) felt better, 3 were unaffected, and

6 were worse. Pruritus was really troublesome in 8, of whom 6 (75 per cent) were improved. Pain which occurred chiefly with bone lesions and mediastinal and intra-abdominal lymphadenopathy, and which was sometimes related to taking alcohol, was relieved in 10 out of 11 patients.

Objective improvement was assessed by fever, weight-loss, and the change in size of lymph-nodes and the spleen. Fourteen patients had fever which was observed while in hospital, and in 13 the fever abated after treatment with cyclophosphamide; this is probably an unrealistic result as the fever is usually undulant or relapsing in type and tends to remit

Table I. Initial Results of Treatment with Cyclophosphamide in 62 Patients with Hodgkin's Disease

Result of Treatment	Number of Patients
Beneficial	43 (69 per cent)
Clinical state unchanged	6 (10 per cent)
Failed—Clinical deterioration Treatment abandoned	9 (15 per cent) 4 (6 per cent)
Total number of patients	62

Table II. Analysis of the Effect of Cyclophosphamide on Various Symptoms and Signs in 58 Patients with Hodgkin's Disease

	Manifestation of Disease	Number of Patients	Better	Unchanged	Worse
Subjective	Malaise	29	20	3	6
	Pruritus	8	6	2	—
	Pain	11	10	—	1
Objective	Fever	14	13	1	—
	Weight-loss	19	13	5	1
	Enlargement of lymph-nodes and spleen	49	33	7	9

spontaneously. Weight-loss was significant in 19 patients and of these 13 (approximately 70 per cent) gained weight with treatment, 5 being unchanged, and 1 continuing to lose. In 49 patients there was significant enlargement of superficial lymph-nodes or the spleen when treatment with cyclophosphamide was started, and in 33 (67 per cent) there was a reduction in size, but no change in 7, and progressive enlargement in 9.

In addition to these common manifestations of the disease, cyclophosphamide also proved effective in the treatment of bone lesions, and in 1 patient with massive infiltration of the kidney the size of the mass was considerably reduced. Radiographs showed recalcification of osteolytic lesions in both the skull and one of the ribs in another patient.

From this there can be no doubt that when cyclophosphamide is used for the first time in patients with Hodgkin's disease it is likely to prove effective. Occasionally the improvement is dramatic, as with 1 patient who was started on the drug in December 1959, when she was moribund, and who is now not only alive but active and feels well.

Indications for using Cyclophosphamide in Hodgkin's Disease

We have used cyclophosphamide alone and also in combination with radiotherapy and corticosteroids in the management of patients with Hodgkin's disease. The response is variable and depends essentially on two things: the previous treatment and the stage of the disease. If patients have never received any form of nitrogen mustard in the past they almost invariably respond well the first time it is given, whether one uses mustine hydrochloride, chlorambucil, or cyclophosphamide. However, after a variable period of time the disease becomes resistant to these compounds. There is also no doubt that with advanced disease they are less effective.

It has been our practice to treat localized Hodgkin's disease with radiotherapy and to reserve treatment with cyclophosphamide for widespread disease. Large glandular masses usually respond better to radiotherapy than to chemotherapy and therefore, with patients who have massive lesions and generalized disease, radiotherapy to the major lesions has been followed by cyclophosphamide to bring the disease under control. Because of the effect on the blood-count we usually do not give cyclophosphamide at the same time as radiotherapy but use these forms of treatment consecutively.

Cyclophosphamide has also proved of benefit in conjunction with corticosteroids. For example, in patients with Hodgkin's disease who also have a haemolytic anaemia or severe malaise the combination has proved most helpful.

Comparison with other Nitrogen Mustards

During recent years we have used three forms of nitrogen mustard: mustine hydrochloride, chlorambucil, and cyclophosphamide.

The advantages and disadvantages of mustine hydrochloride are well known. Its chief use lies in the fact that it has a rapid action, but its disadvantages are that it has to be given by infusion into a fast-running drip and almost invariably causes considerable nausea and vomiting.

Chlorambucil has the advantage that it is given orally but, in our experience, there is a limit to the length of time during which this drug can be administered because of its effect on the leucocyte and platelet counts.

Cyclophosphamide has the great advantage that it can be given intravenously, into serous cavities, or orally, although its action even when injected is not as rapid as that of mustine hydrochloride. It can, however, be given for long periods of time, and we have several patients who have been taking it for three years without ill-effects. Its disadvantages include loss of hair, depression of the leucocyte and platelet counts, and occasionally anorexia, nausea, vomiting, and haemorrhagic cystitis. These side-effects usually disappear rapidly when the drug is stopped.

We now use only two forms of nitrogen mustard in Hodgkin's disease: mustine hydrochloride which is reserved for patients in whom a response is needed within a matter of hours, for example, with tracheal obstruction or spinal cord compression; and cyclophosphamide which is used on all other occasions. For a rapid response, i.e., within days or weeks, the drug is given by intravenous injection and, if a slower response is acceptable, it is given by mouth.

Acknowledgement

These results are based on an analysis of cases under the care of Sir Ronald Bodley Scott to whom I am most grateful for all his help, encouragement, and advice.

DR. J. B. HEALY (*St. Luke's Hospital, Dublin*)

Hodgkin's Disease

A man of 50 was treated with cyclophosphamide in another hospital for Hodgkin's disease presenting as enlarged glands in the neck. The glands had regressed and he had been discharged home on 100 mg. cyclophosphamide daily.

During the following 11 months he attended hospital only once for a white count. On admission to St. Luke's Hospital the white-cell count was 4200 after a year's uncontrolled treatment. He died a few days after admission and the cause of death was thought to be heart failure. At post-mortem there was marked centrilobular necrosis of the liver, which may have been partly attributable to cyclophosphamide.

LYMPHOSARCOMA

DR. W. B. DAWSON (*The Liverpool Radium Institute*)

Some Considerations regarding the Management of Lymphosarcoma and Hodgkin's Disease

There is evidence that cure may sometimes follow X-ray therapy to localized cases of Hodgkin's disease and lymphosarcoma (Easson and Russell, 1963). Our policy, based on this conception, is to treat early cases by X-rays alone; we believe that nitrogen mustards are never curative and should be reserved for the later stages: we can find no place for them in the treatment of the localized disease.

The considerations involved in the management of the two diseases in their advanced stages are slightly different and must be considered separately.

Lymphosarcoma

Lymphosarcoma can show all degrees of response to chemotherapy. While in some cases the results of treatment are dramatic, in others there may be no distinguishable effect whatsoever, a range of sensitivity which is also shown to X-rays and which supports a

Easson, E. C., and Russell, M. K. (1963), *Brit. med. J.*, 1, 1707.

clinical impression that the histological picture of 'lymphosarcoma' may be common to a variety of possibly unrelated disorders.

Treatment of the sensitive case can result in complete disappearance of huge tumour masses in a very short space of time; conventional mustine, however, can produce severe toxaemia (probably due to rapid tumour disintegration) and marrow damage: we prefer cyclophosphamide in these cases because of its more gradual action and lower toxicity. The following two brief case histories illustrate these points.

Case 1. Mrs. M. G., aged 46 years. Presented in September, 1955, with enlarged glands in both sides of the neck which had been noticed 6 months previously, biopsy of which had been reported as 'lymphosarcoma'. She was treated by X-ray therapy, the enlarged glands disappearing completely. She kept well until April, 1961, when she developed grossly enlarged iliac and inguinal lymph-glands. In July, 1961, an epigastric mass was palpated but she refused to come into hospital until February, 1962, when she was seriously incapacitated by gross oedema of the right leg. She was treated by intravenous cyclophosphamide (6 g. in 3 weeks), which produced complete tumour regression, the only toxic manifestation being temporary epilation, and she remains well to date.

Case 2. F. R., aged 16 years. In May, 1953, a mass was excised from this patient's right orbit, when a histological diagnosis of 'benign lymphoma' was made: local recurrences were excised in September, 1953, March and August, 1954: on the last occasion the histological picture was 'lymphosarcoma'. A further recurrence occasioned his reference to us for radiotherapy in October, 1954: by this time there was an enlarged gland in the right upper neck. The right side of the neck and the orbit were irradiated with complete tumour regression, and there was no further development until January, 1962, when he developed an enlarged gland in the left lower neck, which was also effectively treated by X-rays. In February, 1963, he developed multiple glandular enlargement with hepato- and splenomegaly and gross oedema of the lower limbs. He looked toxic but refused to come to hospital, and was treated as an out-patient by oral cyclophosphamide over the next 4 months, starting with 200 mg. daily and reducing doses, to a total of 18 g. He was without apparent disease in June when treatment was stopped: in August he had slight enlargement of the groin glands which, if progressive, will shortly indicate a resumption of cyclophosphamide therapy, and it may be that he will have to remain permanently on the drug.

In such a case, showing an early tendency to recurrence, it is an advantage to be able to exert continued tumour suppression over long periods. Intravenous preparations present difficulties in administration, and chlorambucil, which we have used previously in such cases, is apt to produce irreversible marrow damage which we have not yet observed with cyclophosphamide.

Hodgkin's Disease

The large glandular and visceral masses of Hodgkin's disease rarely, if ever, show the same dramatic response as those of lymphosarcoma, and we believe the ideal case for chemotherapy is the patient with minimal glandular and visceral enlargement and maximal toxicity, expressed as pyrexia, pruritus, or haemolytic anaemia. We continued to use conventional mustine because of the immediate and dramatic relief obtained in such cases: unfortunately this effect is often short-lived, lasting usually two or three months, and we

now attempt to protract palliation by giving oral cyclophosphamide as soon after mustine as the blood-picture allows, and continue its administration indefinitely. In the few cases so treated we have felt that the palliative effect was extended longer with a combination of cyclophosphamide and mustine than might have been expected with either mustine alone or cyclophosphamide alone. We have not seen epilation, probably because a lower dosage of cyclophosphamide is required when another agent is employed for initial chemotherapy.

The following two case histories are illustrative.

Case 3. D. R., aged 19 years. This patient was referred in March, 1961, having been investigated elsewhere for anaemia. Biopsy of a cervical gland was reported as 'Hodgkin's sarcoma'. He was toxic and pyrexial. There were slightly enlarged glands in the left lower neck and mediastinum. Liver and spleen were just palpable, and his haemoglobin level was 57 per cent. Sternal puncture showed an active normoblastic marrow. He was given 24 mg. of mustine intravenously, and the neck and mediastinum were irradiated. He remained apyrexial and free from glandular and visceral enlargement, but the haemoglobin level showed only a temporary rise to around 65 per cent, and in September had fallen to 50 per cent. Radioactive tracer studies at this stage showed increased haemolysis with mild hypersplenism. On treatment with chlorambucil the haemoglobin level rose to 78 per cent in January, 1962, when the drug was stopped: the level continued to rise to a peak of 93 per cent in April but then fell steadily to 52 per cent by January, 1963. Response to a further dose of mustine was, inexplicably, more pronounced than on the previous occasion and 6 weeks later the haemoglobin level had risen to 80 per cent, when treatment with oral cyclophosphamide was instituted. Since then he has remained on this drug and the level is sustained at around the 95 per cent mark. His general condition is excellent: there are no signs of active disease: to date he has had 15 g. of cyclophosphamide.

Case 4. D. J. F., aged 36 years. When first seen by us in July, 1962, this patient gave a 3 years' history of dermatitis associated with severe pruritus and troublesome sweating. Recently a mass of glands had appeared in the neck, biopsy of which had been reported as 'Hodgkin's disease'. He was pyrexial, and had slight generalized glandular enlargement. He was treated by an intravenous dose of mustine: the pyrexia settled immediately, and 2 months later he was practically free from symptoms and all enlarged glands had regressed. As in our experience improvement in such cases rarely lasts long, we decided to anticipate deterioration and gave cyclophosphamide, initially by both oral and intravenous routes and later orally only. A mass of glands appeared in the left axilla and was successfully irradiated in December, 1962.

At present he is symptom-free. He has a number of slightly enlarged glands in the neck. He has had a total dosage of 39 g. cyclophosphamide over 11 months, of which 5 g. have been given intravenously, the remainder orally.

DR. J. S. MALPAS (*Radcliffe Infirmary, Oxford*)

Lymphosarcoma

A woman of 40 years was admitted in April, 1963, following 3 months' loss of weight with alteration in bowel habit. Just before admission she had become temporarily obstructed. On examination, she had bilateral pleural effusions, and a distended abdomen with ascites. A rounded mass was felt on rectal examination.

A biopsy was taken from this mass and proved to be lymphosarcomatous. A barium enema showed a filling defect above the rectosigmoid junction, and a smaller lesion higher up.