PRELIMINARY COMMUNICATIONS

Adriamycin in the Treatment of Acute Leukaemia

J. M. A. WHITEHOUSE, D. CROWTHER,
C. J. T. BATEMAN, M. E. J. BEARD, J. S. MALPAS

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Summary

In a preliminary study a new antitumour antibiotic, adriamycin, was found to be capable of inducing complete remission in 6 out of 17 patients with acute lymphoblastic leukaemia and in one out of four with lymphoblastic lymphosarcoma despite the fact that these patients had either failed to respond or had relapsed after chemotherapy with agents recognized to be potentially successful in each condition. In five cases of acute lymphoblastic leukaemia adriamycin was used in combination with cytosine arabinoside—three achieved complete remission and two good partial remissions. This combination seems to merit further study in patients who have relapsed on the more conventional chemotherapeutic regimens in acute lymphoblastic leukaemia.

In 13 patients with acute myelogenous leukaemia previously treated with daunorubicin and cytosine arabinoside no remissions were obtained with the dose range used.

Introduction

A new antitumour antibiotic, adriamycin, was isolated from a mutant of *Streptomyces peucetius* in 1967. Structurally similar to daunorubicin, it differs only in the substitution of a hydroxyl group for a hydrogen atom in an acetyl radical. The success of daunorubicin in the treatment of the acute leukaemias (Crowther *et al.*, 1970) and the reported success of adriamycin (Bonadonna *et al.*, 1969) in the treatment of childhood tumours suggested that a trial of adriamycin in acute leukaemia was indicated.

The cases reported in this paper presented with lymphoblastic leukaemia, acute myelogenous leukaemia, or lymphoblastic lymphosarcoma. They received adriamycin after failing to respond to chemotherapy with agents recognized to be potentially successful in those conditions, or when they relapsed following successful therapy.

Patients Treated

The 35 patients so far included in the trial consisted of 17 (aged 2 to 58) with acute lymphoblastic anaemia, one with acute prolymphocytic leukaemia, 13 (aged 13 to 73) with acute myelo-

genous leukaemia, and four (aged 14 to 41) with lymphoblastic lymphosarcoma.

Because of the proved efficacy of vincristine and prednisolone (Hardisty *et al.*, 1969) in combination in acute lymphoblastic leukaemia and of daunorubicin and cytosine arabinoside (Crowther *et al.*, 1970) in acute myelogenous leukaemia, these agents were always used first and adriamycin substituted only when relapse occurred or when complete remission could not be achieved following their use. Furthermore, the improved results produced by combination chemotherapy compared with the use of a single agent alone made us reluctant to use adriamycin alone, so that in many cases of acute lymphoblastic leukaemia prednisolone or cytosine arabinoside was used concurrently and in acute myelogenous leukaemia adriamycin was given with cytosine arabinoside, thioguanine, or mercaptopurine.

Adriamycin is supplied as a red crystalline powder in vials containing 20 mg. It is readily soluble in water for injection and was given in courses of two to three days, a dose of 0.4 mg/kg being used as a single intravenous injection daily.

A full blood count including white count, differential count, and platelet count was performed on alternate days during treatment, and because of previous experience with the antitumour antibiotic daunorubicin (Malpas and Scott, 1968, 1969) electrocardiograms were taken before and during therapy. All patients receiving treatment were given allopurinol 100 mg thrice daily, the dose of mercaptopurine, when given, being adjusted accordingly.

If infection occurred antibiotic therapy was begun immediately after appropriate attempts to identify the organism but without awaiting the results of the cultures.

Remission was regarded as complete only when the patient had no symptoms or physical signs, had a normal peripheral blood, and when bone marrow examination showed a normocellular marrow containing no abnormal primitive cells.

Results

Of the 17 patients with acute lymphoblastic leukaemia treated with adriamycin, six achieved complete remission (Tables I and II). In two of these (Cases 2 and 8) a further complete remission was obtained after additional adriamycin therapy. It is of interest that Case 8 had had a previous complete remission induced with daunorubicin. In another patient (Case 10) three courses of vincristine and prednisolone failed to induce a complete remission; adriamycin was subsequently substituted for vincristine to a total dose of 150 mg. This resulted in severe bone marrow hypoplasia but was followed by a complete remission.

A complete remission was rapidly obtained in Case 2 with a dose of 120 mg of adriamycin, a three-day course being combined with a five-day course of cytosine arabinoside. Five cases of acute lymphoblastic leukaemia were treated with this combination, producing three complete remissions and two good partial remissions. These promising results suggest that the combination merits further investigation.

Only one of the 13 cases of acute myelogenous leukaemia achieved a partial remission. No complete remission followed the administration of adriamycin to these patients, but all had previously received intensive treatment with daunorubicin. In four patients with lymphoblastic lymphosarcoma one complete remission occurred (Case 20). This patient had had extensive previous chemotherapy resulting in a partial remission and then converted to complete remission with a total dose of 150 mg of adriamycin given in combination with cytosine arabinoside. One

I.C.R.F. Department of Medical Oncology, St. Bartholomew's Hospital, London

J. M. A. WHITEHOUSE, M.B., M.R.C.P., Clinical Assistant

D. CROWTHER, M.B., M.R.C.P., Physician

C. J. T. BATEMAN, B.M., B.CH., M.R.C.PATH., Senior Registrar, Department of Haematology

M. E. J. BEARD, M.B., M.R.C.PATH., Consultant Haematologist

J. S. MALPAS, M.B., F.R.C.P., Senior Lecturer in Medicine

TABLE I—Patients with Acute Leukaemia Treated with Adriamycin

Case No.	Age and Sex	Diagnosis*	Previous Therapy†	Concurrent Therapy†	Total Dose (mg)	Results ‡	Comments
1	14 M.	A.L.L.	P.VCR.MTX.	P.AraC.	140	P.R.	
2	18 F.	A.L.L.	P.VCR.MTX.	AraC.	300	C.R.	Two successive C.R.s
3	5 M.	A.L.L.	P.MP.MTX.VCR.		30	Died	
4	47 F.	A.L.L.	P.VCR.AraC.DR.MTX.		150	P.R.	C.R. then failed DR. therapy before A.
5	17 M.	A.L.L.	P.VCR.AraC.DR.	P.	300	P.R.	
6	38 M.	A.L.L.	P.MP.VCR.CY.DR.	P.MP.	90	F.	Hypoplastic before A.
7	58 F.	A.L.L.	P.VCR.MTX.MP.As.	P.	130	F.	
8	12 M.	A.L.L.	VCR.P.MTX.MP.AraC.	T. with 2nd C.R.	510	C.R.	Two successive C.R.s on A. after two C.R.s with DR.
9	12 M.	A.L.L.	MP.P.VCR.CY.MTX.				
			AraC. DR	P.	140	F.	Hypoplastic
10	20 F.	A.L.L.	P.VCR.failed	P.	150	C.R.	
11	13 F.	A.L.L.	VCR.P.failed	AraC.	180	C.R.	
12	19 M.	A.L.L.	VCR.P.MTX.	AraC.	300	C.R.	
13	2 F.	A.L.L.	VCR.P.MP.MTX.As.		32	P.R.	
14	18 F.	A.L.L.	P.VCR.	P.	180	F.	Spleen reduced in size
15	15 F.	A.L.L.	P.VCR.DR.AraC.MTX.	P.	300	C.R.	Severe stomatitis
16	22 M.	A.L.L.	P.VCR.DR.	T.	150	F.	Hypoplastic
17	25 F.	A.L.L.	P.VCR.	AraC.	60	P.R.	
18	20 M.	A.P.L.L.	VCR.P.DXR.	T.	60	F.	
19	26 M.	L./L.S.A.	HN2.N.P.VCR.	T.	20	F.	Died with staphylococcal septicaemia but not pancytopenia due to A.
20	21 F.	L./L.S.A.	VCR.P.MTX.	AraC.	150	C.R.	A. converted P.R. to C.R.
21	41 F.	L./L.S.A.	DXR.QT.	AraC.	180	F.	
22	14 M.	L./L.S.A.	DXR.VCR.P.	P.AraC.	240	P.R.	
23	61 M.	A.M.L.	DR.AraC.	AraC.	50	P.R.	
24	34 M.	A.M.L.	MP.P.As.DR.AraC.T.	AraC.	100	F.	
25	13 F.	A.M.L.	DR.AraC.	MP.	60	F.	
26	38 F.	A.M.L.	DR.AraC.As.	MP.	150	F.	
27	45 F.	A.M.L.	P.VCR.MP.DR.AraC.	AraC.	120	F.	Reduction in the blasts in the bone marrow
28	15 M.	A.M.L.	DR.P.VCR.AraC.	—	60	F.	Fall in blast count
29	21 M.	A.M.L.	VCR.P.AraC.DR.MTX.	T.	225	F.	
30	58 M.	A.M.L.	DR.AraC.	T.	60	F.	Fall in blast count
31	36 M.	A.M.L.	DR.AraC.MP.MTX.CY.P.	T.	60	F.	
32	54 M.	A.M.L.	P.CY.DR.AraC.MTX.	T.	160	F.	
33	71 F.	A.M.L.	DR.AraC.	T.	120	F.	Fall in blast count
34	73 F.	A.M.L.	DR.AraC.	T.	50	F.	
35	21 F.	A.M.L.	As.DR.AraC.	MP.	60	F.	

* A.L.L. = Acute lymphoblastic leukaemia. A.M.L. = Acute myelogenous leukaemia. L./L.S.A. = Lymphoblastic lymphosarcoma. A.P.L.L. = Acute prolymphocytic leukaemia.

† A. = Adriamycin. As. = Asparaginase. AraC. = Cytosine arabinoside. CY. = Cyclophosphamide. DR. = Daunorubicin. MP. = Mercaptopurine. MTX. = Methotrexate. P. = Prednisolone. T. = Thioguanine. N. = Natulan. HN2. = Nitrogen mustard. VCR. = Vincristine. Q.T. = Quadruple chemotherapy (HN2.N.VCR.P.). DXR. = Radiotherapy.

‡ C.R. = Complete remission. P.R. = Partial remission. F. = Failure.

TABLE II—Adriamycin in Acute Leukaemia

Diagnosis	No. of Cases	Results
Acute lymphoblastic leukaemia	17	{ 6 Complete remission 5 Partial remission 6 Failed
Acute prolymphocytic leukaemia	1	{ 1 Failed
Acute myelogenous leukaemia	13	{ 1 Partial remission 12 Failed
Lymphoblastic lymphosarcoma	4	{ 1 Complete remission 1 Partial remission 2 Failed

partial remission was also obtained—Case 22. One case of acute prolymphocytic leukaemia failed to respond to a total of 60 mg of adriamycin given in combination with thioguanine.

The major complications of adriamycin are reported to be severe bone marrow depression, stomatitis, alopecia, and E.C.G. changes. Although adriamycin seemed to have a rapid and pronounced effect on the peripheral blood count, and pancytopenia and marrow hypoplasia were seen in the patients treated, no deaths attributable to haemorrhage or sepsis occurred. One child had E.C.G. changes after a course of daunorubicin. No further change was noted after adriamycin. Stomatitis was seen in a number of cases, but was no more severe than that seen after therapy with daunorubicin. It is possible that the absence of changes in the electrocardiogram and the low incidence of severe stomatitis compared with that reported in other series are related to the modified dose regimen used here.

Alopecia was frequent and severe. Its occurrence did not seem to be related to the dose of adriamycin.

Discussion

Adriamycin can produce remission in acute lymphoblastic leukaemia and lymphoblastic lymphosarcoma. In acute lymphoblastic leukaemia it forms a very useful second-line drug

which may be substituted for vincristine either in the event of the failure of remission induction by conventional methods or when relapse has occurred. It would seem to be most effective when used in combination with cytosine arabinoside. In one of our cases cross-resistance between daunorubicin and adriamycin was not apparent, for after a further attempt to achieve remission with daunorubicin failed a rapid and successful complete remission was achieved with adriamycin. This one example of the apparent absence of cross-resistance between these closely related agents will require further confirmation.

The disappointing results in acute myelogenous leukaemia would suggest that either the present regimen was not intensive enough to achieve complete remission or that all the patients who had previously received daunorubicin had myeloblasts at subsequent relapse insensitive to the second drug. Certainly Mathé *et al.* (1970) were able to obtain six complete remissions in 18 patients with acute myelogenous leukaemia but noted that four patients previously treated with daunorubicin failed to benefit from adriamycin.

A comparative trial of adriamycin and daunorubicin in the treatment of acute myelogenous leukaemia will be necessary, however, to decide this question finally.

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