CLINICAL RESEARCH

Membrane phenotype and response to deoxycoformycin in mature T cell malignancies

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Abstract

The adenosine deaminase inhibitor deoxycoformycin was used in low doses to treat 19 patients with clinically aggressive T cell malignancy with a mature membrane phenotype. The patients comprised eight with prolymphocytic leukaemia, two with chronic lymphocytic leukaemia, four with adult T cell leukaemia-lymphoma, three with Sézary syndrome, and two with T cell lymphoma. Two thirds of the patients had been resistant or minimally responsive to combination chemotherapy. Complete remission was obtained in five patients (two with prolymphocytic leukaemia and one each with chronic lymphocytic leukaemia, adult T cell leukaemia-lymphoma, and Sézary syndrome) and partial remission in two others. Unmaintained complete remission lasting more than one year was seen in three patients.

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Responses were obtained only in patients with CD4+, CD8- membrane markers (seven out of 10), and no responses were recorded in any of the nine patients with a different phenotype.

In this series remission appeared to correlate with the membrane phenotype of the neoplastic cell and not with the cytopathological diagnosis. Future studies should establish the biochemical basis for the greater sensitivity of CD4+ lymphoid cells to deoxycoformycin.

Introduction

The treatment of mature T cell malignancies has been disappointing. The median survival in two of the most common disorders (T prolymphocytic leukaemia and adult T cell leukaemia-lymphoma) is six and five months, respectively. Deoxycoformycin (Pentostatin), a potent inhibitor of adenosine deaminase, has been used to treat patients with a wide range of lymphoid neoplasms with variable success.¹ Differences in sensitivity among the various diseases may relate to the cellular activity of enzymes concerned with purine metabolism. The high levels of activity of adenosine deaminase in T cells as compared with B lymphocytes provided a rationale for treating T cell malignancies with deoxycoformycin.² Other evidence, however, shows that cases with low levels of adenosine deaminase activity—for example, hairy cells and other malignant B cells—also respond to deoxycoformycin.^{1,3,4} At present there is no definitive biochemical or membrane marker which identifies those cell types that are likely to respond or be resistant to deoxycoformycin. Plainly identifying such a marker would be of clinical advantage.

We report the response to deoxycoformycin in 19 patients with clinically aggressive T cell malignancies characterised by a mature (post-thymic) membrane phenotype (TdT-, CD1-).

Patients and methods

The 19 patients (age range 29-82 (median 56) years) comprised eight with T cell prolymphocytic leukaemia, two with T cell chronic lymphocytic

leukaemia (clonal proliferation of large granular T lymphocytes), four with human T cell leukaemia virus type I positive adult T cell leukaemia-lymphoma, three with Sézary syndrome, and two with T cell lymphoma. Twelve of the patients were resistant or had been minimally responsive to intensive combination chemotherapy which included cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, and dexamethasone.

Before beginning deoxycoformycin diagnostic material was reviewed and the membrane phenotype evaluated with an extensive range of monoclonal antibodies. Morphological diagnosis of cell type was confirmed by electron microscopy in all cases. Renal and hepatic function was assessed before treatment and weekly throughout. Baseline renal function (creatinine clearance) was normal in all cases.

Deoxycoformycin was provided by the United States National Cancer Institute for use within the restrictions of a protocol approved by the National Cancer Institute and the local research ethics committee at Hammersmith Hospital. It was supplied as a sterile lyophilised powder, reconstituted with physiological saline to a concentration of 2 g/l, and given in a dose of 4 mg/m² by slow intravenous injection weekly or twice weekly with a range of 2-20 (mean 6) injections. Treatment was stopped once a complete remission or the best positive response was achieved. No maintenance treatment was given to patients with complete remission. Allopurinol and prophylactic antibiotics (co-trimoxazole and oral amphotericin) were given during treatment.

Results

Complete remission was recorded in five patients (two with T cell prolymphocytic leukaemia (cases 2 and 7) and one each with T cell chronic lymphocytic leukaemia (case 10), adult T cell leukaemia-lymphoma (case 11), and Sézary syndrome (case 15)) and partial responses in two (both with T cell prolymphocytic leukaemia (cases 5 and 6; table)). Minor or no responses were recorded in the other 12 patients. Three of these patients, however (cases 4, 18, and 19), died within a few weeks of starting treatment before a response could be fully evaluated. One patient (case 4) died of active disease having received four injections of deoxycoformycin which had resulted in a fall in his white cell count from 300 to 25 × 10⁹/l. Eight of the remaining nine non-responders subsequently died of advanced disease.

Of the five patients achieving complete remission, three (cases 2, 7, and 10) relapsed; two of these (cases 7 and 10) responded again to deoxycoformycin, though in case 7 the second response was partial and short lived (figure). The remaining patient (case 2) died from chest infection and cardiac failure before deoxycoformycin could be reintroduced. One patient with adult T cell leukaemia-lymphoma (case 11) died of an opportunistic infection while still in complete remission. In case 15 (Sézary syndrome) the patient was still in her first complete remission nearly three years after stopping all treatment. This patient had been resistant to cytotoxic chemotherapy and was in a poor clinical state when she began deoxycoformycin. She received a total of 12 injections over three months. Her clinical response to deoxycoformycin was therefore dramatic and sustained.

Two patients achieved a partial response; one (case 5) relapsed during treatment and died of advanced disease 15 months after beginning

Case 7. Haematological chart showing two responses to deoxycoformycin. (CHOP=Cyclophosphamide, doxorubicin, vincristine, prednisone.)

deoxycoformycin, and the other (case 6) died of infectious complications six months after starting treatment with deoxycoformycin.

Complete remission thus occurred in five of 10 patients with a CD4+,CD8- membrane phenotype, two other such patients achieving partial remission. No responses were recorded in patients with CD4+,CD8+ or CD4-,CD8+ or CD4-,CD8- phenotypes. This difference was significant ($p < 0.03$; Fisher's exact test).

The severe toxic effects on liver, kidneys, and central nervous system seen in early studies with deoxycoformycin in which high dose regimens were employed^{2,6} did not occur in our series. Deoxycoformycin was tolerated very well by all the patients, with no appreciable abnormality seen in renal or hepatic function. Five patients had no side effects at all. Mild nausea and lethargy occurred in 12. Two patients developed profound neutropenia, and one (case 4) also had thrombocytopenia. Both patients subsequently developed fatal infections.

Discussion

This study has shown a significant difference in response to deoxycoformycin between mature T cell malignancies characterised

Details of patients and outcome of treatment with deoxycoformycin

Case No	Age (years)	Sex	Diagnosis	Membrane phenotype*	Response to deoxycoformycin	Follow up
1	56	M	TPLL	CD4+,CD8+	NR	Died nine months later
2	82	M	TPLL	CD4+	CR	Relapsed after 18 months and died
3	49	M	TPLL	CD4+,CD8+	NR	Died six months later
4	69	M	TPLL	CD4+	NR	Died after three weeks of deoxycoformycin
5	74	M	TPLL	CD4+	PR	Relapsed during treatment with deoxycoformycin and died
6	57	M	TPLL	CD4+	PR	Died (infection)
7	61	M	TPLL	CD4+	CR	Relapsed after six months and had short partial remission with deoxycoformycin
8	78	F	TPLL	CD4+	NR	Still alive eight months later
9	61	M	TCLL	CD8+,CD11b+	NR	Died
10	64	M	TCLL	CD4+,CD11b+	CR	Relapsed after 23 months; responded again to deoxycoformycin
11	45	M	ATLL	CD4+	CR	Died in complete remission (opportunistic infection)
12	35	F	ATLL	CD4+	NR	Died four months later
13	35	F	ATLL	CD4+,CD8+	NR	Died
14	29	M	ATLL	CD4-,CD8+	NR	Died two months later
15	31	F	SS	CD4+	CR	Thirty four months in complete remission
16	80	F	SS	CD16+	NR	Died two months later
17	48	F	SS	CD8+,CD4-	NR	Died nine months later
18	43	F	T Cell lymphoma	CD4+,CD8+	NR	Died after three weeks of deoxycoformycin
19	36	M	T Cell lymphoma	CD4+,CD8+	NR	Died after one month of deoxycoformycin

TPLL=T Cell prolymphocytic leukaemia. TCLL=T Cell chronic lymphocytic leukaemia. ATLL=Adult T cell leukaemia-lymphoma. SS=Sézary syndrome. NR=No response. CR=Complete remission. PR=Partial remission.

*Cells in all cases were CD1 and TdT negative and reactive with other pan T monoclonal antibodies. Results of CD4 (OKT4) and CD8 (OKT8) if not shown were negative.

by a CD4+ membrane phenotype and those characterised by any other membrane phenotype. The reason for this difference is not clearly understood.

Deoxycoformycin inhibits adenosine deaminase, thereby causing deoxyadenosine and deoxyadenosine triphosphate to accumulate within the cell. In rapidly proliferating cells deoxyadenosine triphosphate is thought to cause cell death by inhibiting ribonucleotide reductase. In resting cells breaks appear in the strands of the deoxyribonucleic acid, possibly associated with toxicity.⁷ 5'-Nucleotidase, which degrades deoxynucleotide triphosphates, diphosphates, and monophosphates to deoxynucleosides, may prevent the accumulation of deoxyadenosine triphosphate in the cell caused by deoxycoformycin.⁸ It seems likely, therefore, that low levels of 5'-nucleotidase activity would make cells more vulnerable to the toxic effects of deoxycoformycin. Massaia *et al* reported that CD4+ lymphocytes have significantly less 5'-nucleotidase activity than CD8+ lymphocytes.⁹ Indeed, CD8+ lymphocytes have similar levels of activity to normal B cells, which are not generally killed by deoxycoformycin. This difference in levels of 5'-nucleotidase activity between CD4+ and CD8+ cells is consistent with our finding that T cell leukaemias characterised by CD4+, CD8- cells respond more favourably to deoxycoformycin. On the other hand, Ma *et al* reported that there was no significant difference in the activities of adenosine deaminase and 5'-nucleotidase between CD4+ and CD8+ cases of T cell chronic leukaemia.¹⁰ Their series was small, however, and did not include observations on the effect of deoxycoformycin. It would clearly be of interest to measure the activities of those enzymes in a larger series of T cell malignancies to see if any correlation could be found between the activity of 5'-nucleotidase and the response to treatment with deoxycoformycin.

Though the responses in our patients with mature T cell leukaemia showed a correlation with the membrane phenotype, there was none with the various cytopathological types of T cell leukaemia. These observations, if confirmed by further laboratory and clinical studies, might help define the indications for using deoxycoformycin in refractory lymphoid malignancies.

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ONE HUNDRED YEARS AGO

The annual meeting of the "subscribers, donors, governors, and friends" of this hospital recently held, was naturally the scene of lively discussion. As not infrequently happens in heterogeneous assemblies, animated by various sentiments, and imperfectly informed as to the subject-matters, the decisions arrived at were the outcome of passion rather than of reason. Nothing could be in better or more judicial spirit than the opening speech of the chairman, Mr T A Bushby. Having traced briefly the history of the late proceedings in connection with the operations performed by Dr Imlach, he emphasised the difficulty that must embarrass a tribunal chosen by accident more than for any special competency, in its endeavour to adjudicate upon a controversial question of science and practice. He quoted the following passage from the remarks made in the JOURNAL of January 18th: "The governors cannot be expected to pass a definite and conclusive judgment upon an operation new to surgical science, not yet adequately known even to the medical profession, and one which has not emerged from the storm of opposition let loose by ignorance and prejudice, as well as by less blameable motives." And this question of science and practice seems at the present moment to be so intricately mixed up with personal considerations, that a decision free from objection can hardly be expected. A calm perusal of the report of the meeting leads to the conclusion that the question of science and practice has been overwhelmed, or kept out of sight by the personal considerations involved. The whole question may be stated briefly thus: Is the operation for removal of the uterine appendages justifiable? Has the action of Dr Imlach in advocating and practising this operation been justifiable? The general answer from all sources, endorsed by the governors, to the first question, is in the affirmative. The answer of a majority of the governors to the second question is in the negative. That is to say, in their view it has been wrong for him to do that which is in itself right.

The Chairman showed to what extent personal feelings were mixed up in the affair in these words: "I might have unfolded . . . the curious private history (and guidance afforded to your committee) during the recent troubled times; I might have explained the incongruous personal relations of

the different members of the staff, and the consequent difficulties about consultations, and have shown that the committee were at no period prepared to have given either countenance or effect to the idea that the practice of the hospital was contrary to, or in advance of, the scientific opinion of the day."

It would have been well had the meeting acted in the wise spirit evinced in these words. On the question of re-electing the staff arising, first, Dr Briggs, a new member, was elected unanimously; secondly, Dr Burton, who had been on the staff since the formation of the hospital, and who was pointedly accused by Mr S B Bacon of being "the originator" of the quarrels, was elected by 13 votes to 9; thirdly, when the case of Dr Imlach's re-election came up, it was negatived by 17 to 16 votes. A poll was demanded; and (it seems hard to believe, but so it was) the matter was decided by proxy votes, as at a shareholders' meeting of a public company, and the numbers were—for Dr Imlach, 137; against, 312. No comment is necessary upon such a mode of deciding a scientific or even a personal question. It settles nothing. It only proves the animus and activity of the canvass for proxies. As Mr Malcolm Guthrie, the new Secretary and Treasurer, said, "The character of the meeting was ridiculous, because proxies had been sent out by some persons asking for the power to vote without having heard the speeches. It was like hanging Dr Imlach first and trying him afterwards."

It will be a consolation to Dr Imlach to know that condemnation inflicted in this way can have no possible weight with his professional brethren, or with the disinterested public. He is passing through a storm of obloquy, raised artificially by persons not in a position to judge either him or the surgical operation with which his name is honourably associated. He will, we doubt not, before long find this proxy-judgment reversed by a more competent tribunal, and be reinstated in a position in which he will find opportunity for ample vindication of his personal character, and for the advancement of science, in the cause of which he has suffered so much and so unjustly.

(British Medical Journal 1887;ii:339.)