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2'-Chlorodeoxyadenosine: evaluation of a novel predominantly lymphocyte selective agent in lymphoid malignancies

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Summary 2'-Chlorodeoxyadenosine (2CDA) is a purine analogue selectively active against both resting and dividing lymphoid cells. Twenty-one patients with a variety of previously treated lymphoid malignancies received a total of 41 courses of 2CDA (0.1-0.15 mg/kg/day over 7 days continuous intravenous infusion) on compassionate grounds. The profile of the patient population was as follows: low grade non-Hodgkin's lymphoma (NHL) = 8, intermediate grade NHL = 2, transformed (intermediate grade NHL) = 6, Hodgkin's disease = 1, lymphoplasmacytoid NHL = 3 and lymphoblastic NHL = 1. The overall response rate was 53%, with three patients attaining complete remission (CR) and eight partial remission (PR). Three of 16 patients with primary resistant or resistant recurrent disease entered either CR (1) or PR (2). Ten patients had no response or progressive disease. The latter group was comprised of patients who had extensively pre-treated lymphoplasmacytoid tumours and/or poor performance status (WHO grades 2-4). The median duration of response is 6 months (range 1 to 12 months). Treatment was well tolerated and the chief toxicities were leucopenia and thrombocytopenia which were most pronounced when there was bone marrow involvement. As a result of dose limiting myelotoxicity, a dose escalation to 0.15 mg/kg/day was possible on just three occasions.

These data confirm other reports of the activity of 2CDA in low grade NHL and indicate it may have activity in Hodgkin's disease. There was no demonstrable activity in poor performance status patients or those with extensively pre-treated lymphoplasmacytoid tumours.

2'-Chlorodeoxyadenosine (2CDA) has cytotoxic activity both in resting and dividing cells. Its mechanism of action requires phosphorylation by deoxycytidine kinase and since in the main this enzyme is expressed in lymphocytes, 2CDA has the virtue of primarily being active in lymphoid tissue (Carson *et al.*, 1983). The phosphorylated derivative of 2CDA (CdATP) inhibits ribonucleotide reductase and hence depletes the intracellular pool of deoxynucleotides (Avery *et al.*, 1989). In actively dividing cells DNA synthesis is impaired and this effect is compound by preferential use of CdATP by DNA polymerase with subsequent retardation of chain elongation (Chunduru & Blakley, 1991). The cytopathic mechanism in resting cells may be by induction of programmed cell death since DNA degradation in chronic lymphocytic leukaemia cells incubated with 2CDA is typical of apoptosis (Robertson *et al.*, 1991). The crucial step is thought to be a reduction in NAD. NAD is essential for energy production and its deficiency results in cell death. This may result from the perturbation of the deoxynucleotide pool to produce defective repair of angle-strand breaks in DNA with resultant activation of poly (ADP - ribose) polymerase and consequent consumption of NAD. *In vitro*, the cytotoxic effect of 2CDA can be prevented by restoring the lost NAD by culture with nicotinamide despite the occurrence of strand breaks in DNA (Seto *et al.*, 1985). Other processes may be involved in the action of 2CDA since *in vitro* it inhibits the growth of myeloid progenitor cells in which the levels of deoxycytidine kinase are low (Petzer *et al.*, 1992). Similarly it has activity in acute myeloid leukaemia (Santana *et al.*, 1992) and the main toxicity encountered in clinical trials has been myelosuppression.

A number of phase I and phase I/II studies have investigated the activity of 2CDA in white cell malignancies, the majority having been initiated by the Scripps clinic (Piro, L.D., 1992; Piro *et al.*, 1990; Beutler *et al.*, 1991; Piro *et al.*, 1988; Kahn *et al.*, 1991; Kay *et al.*, 1992). These have shown that 2CDA has promising activity in lymphoid and myeloid malignancies of both high and low grade types. In a recent study, 24 children with refractory leukaemia received 2CDA at 8.9 mg/m^2/day over 5 days. Forty-seven per cent of patients with AML achieved a complete remission with two (12%) achieving partial remission. Only one of seven patients with ALL achieved CR (Santana *et al.*, 1992).

Of the low grade leukaemias excellent activity has been found in hairy cell leukaemia (HCL) with 32 of 45 patients achieving complete remission after a single course of 0.1 mg/kg/day for 7 days (Piro *et al.*, 1990; Beutler *et al.*, 1991). No patient has relapsed and 2CDA seems likely to become the treatment of choice in this disease. In patients with chronic lymphocytic leukaemia (CLL) who received repeated courses of 0.1 mg/kg/day over 7 days, 38 of 89 patients attained a partial remission, with just three patients entering complete remission (Beutler *et al.*, 1991).

The group from the Scripps clinic have also recently described their experience of repeated courses of 2CDA (0.1 mg/kg/day over 7 days) in 40 patients with refractory low grade and transformed low grade non-Hodgkin's lymphoma (Kay *et al.*, 1992). Eight (20%) of patients achieved CR and nine (22.5%) PR. The duration of response ranged from 1 to over 33 months.

Over the past 20 months we have treated 21 patients on compassionate grounds for a variety of lymphoid tumours with 2CDA synthesised in our laboratories.

Materials and methods

To be eligible for treatment patients required a histologically confirmed diagnosis with evaluable disease and who had been previously treated with conventional agents (and in a number of cases; investigational agents). Eight patients had low grade NHL, two intermediate grade NHL, six transformed to intermediate grade NHL, three lymphoplasmacytoid lymphoma, one lymphoblastic NHL and one patient had nodular sclerosing Hodgkin's disease. Details of patients age, sex, histology, stage of disease and previous treatment are shown in

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Table I

Patient	*Age*	*Sex*	*Histology*	*Stage*	*Previous treatment*	*Disease status*	*Bone marrow status*	*Performance status*	*Dose mg/kg/day*	*Response + duration months*	*Grade toxicity*	*Grade toxicity*	*Duration of Tox month(s)*
L.Sh	41	F	'C'	IV A	CB + P	PR	R	+	0	.1	PR	1 Thrombocytopenia	
										.1	PR	1 Thrombocytopenia	
										.1	CR	2 Thrombocytopenia	7[c]
										12[c]		3 Leukopenia	4[c]
L.Sa	49	F	'C'	III A	LOPP	PR	R	–	0	.1	PR	1 Thrombocytopenia	
					CVP	PR				.15	CR	1 Thrombocytopenia	1
					alpha – INF (maintenance)					.1	CR	2 Leukopenia	1
											8	Thrombophlebitis	
JP.T	49	F	'B'	IV A	CVP	CR	R	+	1	.1	PR	4 Thrombocytopenia	
					CB-MP	PR						3 Leukopenia	
					CHOP	PR					8	(Died in PR)	
M.La	39	M	'C'	III A	CB	NC	R	–	0	.1	PR	Thrombophlebitis	
					CVP	PD				.15	PR	1 Thrombocytopenia	
										.1	PR	1 Thrombocytopenia	
										.1	CR	1 Thrombocytopenia	7
											12[c]		
S.B.	21	F	Hodgkin's disease (NS)	III A	LOPP/EVAP	CR	RR	–	2	.1	NC	2 Thrombocytopenia	
					MANTLE RT	CR				.15	PR	4 Thrombocytopenia	8
					C-VAMP	PR					8	3 Leukopenia	
					HDM + ABMT ETOPOSIDE	CR							
					EPIC	PR							
					MP	PD							
					CHLVPP	PD							
D.B.	68	M	Transformed follicular 'C' to large cell + leukemic	IV B	CB	PR	RR	+	1	.1	PR	Died of pseudomonas	
					Splenoctomy							septicemia 4 weeks	NE
				phase	CB/CHOP	PD					Died in PR	post-tx 700 neutrophils	
												3 Thrombocytopenia	
B.M.	55	M	Transformed follicular → 'F'	IV A	RT	CR	RR	+	1	.1	PR	1 Thrombocytopenia	
					CHOP	PR				.1	PR	2 Thrombocytopenia	4[c]
					RT	PR				.1	PR	3 Leukopenia	4[c]
					IMVP16	PR					4[c]	Urticarial rash	
					ETOPOSIDE	PD							
B.B.	70	F	'E'	III A	MBACOD	CR	R	+	1	.1	PR	1 Thrombocytopenia	4[c]
					CB	PR				.1	PR	1 Thrombocytopenia	6[c]
					CB + P	NC						Thrombophlebitis	
					LOPP	PR				.1	PR	2 Leukopenia	
					RICIN IMMUNOTOXIN	NC					6	2 Thrombocytopenia	
L.W.	42	M	'B' ↓ while on 2CDA 'E'	IV A	MBACOD	NC	RR	–	1	.1	PR	Thrombophlebitis	
					PLAT-ETOP	NC				.1	PD		NE
					CB	CR							
					CB + P	PD							
M.Le	42	M	Transformed 'C' to 'G' →	III B	CVP	CR	RR	–	4	.1	PD	Marrow Failure pre-tx	NE
					EPIC	PD						Died	
M.K.	53	F	Lymphoplasmacytoid	IV B	VAPEC-B	NC	1° resistant	+	1	.1	NR	1 Leukopenia	NE
					Fludarabine	NC				.1	PD	1 Leukopenia	
					CB + Pred	NC						1 Thrombocytopenia	
					MACOP	NC							
					E-SHAP	PD							
E.C.	53	M	Waldenstroms	IV B	CB – Pred	NC	1° resistant	+	3	.1	NR	Marrow Failure pre-tx	NE
					VAPEC – B	NC							
					Fludarabine	NC							

Patient	Age	Sex	Histology	Stage	Previous treatment	Disease status	Bone marrow status	Performance status	Dose mg/kg/day	Response + duration months	Grade toxicity	Grade toxicity	Duration of Tox month(s)
L.C.	53	M	Waldenstroms	IV B	Fludarabine	PD	1° resistant	+	2	.1	NR	Marrow Failure pre-tx	
					VAPEC – B	NC				.1	NR	Died	NE
R.B.	39	M	'C'	IV B	COPP	PD	1° resistant	+	2	.1	PD		
					CHOP	PD							
					MACOP – B	PR							NE
					Fludarabine	PD							
					E – SHAP	PD							
D.G.		M	'C'	II	CB	PD	1° resistant	–	0	.1	NR	1 Anaemia	
			nb. Paraprotein		CB	PD							
					CHOP	PD							NE
					Fludarabine								
V.L.	50	M	Transformed 'B'→'F'	IV A	CVP	PR	RR	–	4	.1	PD	Marrow Failure pre-tx	
					M-BACOD	NC						Died	NE
					MP	NC							
					EPIC	PR							
					VC-VAMP	PD							
R.G.	44	M	'D'	IV A	LOPP	PR	RR	+	2	.1	PD	Marrow Failure pre-tx	
					M-BACOD	PR						Died	NE
					JMVP16	NC							
					CHOP	PR							
					ESHAP	PR							
					MP-EPIC	PD							
K.K.	50	F	'C'	IV B	CB + P	PR	RR	+	1	.1	PR	4 Leukopenia	2[c]
					CVP						4	2 Thrombocytopenia	2[c]
					CHOP	PR			3				
					CB	PR-PD							
P.M.	45	M	'B'	III	LOPP	NC	R						
					CHOP	PR		–	0	.1	RR	1 Thrombocytopenia	<1
					IMVP-16	PR					PR	1 Thrombocytopenia	<1
											PR	1 Thrombocytopenia	
											2[c]		
G.D.	51	M	'C' –	IV B	LOPP	CR	RR	–	2	.1	PD	NE	NE
			transformed to G		LOPP	PD						Died	
					MACOP-B	PR							
					CB + P	PD							
					CYCLO-P	PR							
					MACOP-B	PR							
					EPIC	PD							
J.L.	54	M	'J'	IV B	PROMACE-	CR	R	+	1	.1	PR		
					CYTABOM					.1	PR	4 Leukopenia	
					HI-COM	CR				.1	PR	3 Thrombocytopenia	1[c]

Key to abbreviations: CR: A complete response was obtained with prior chemotherapy; PR: A partial response with prior chemotherapy; R: Relapse; RR = Resistant relapse: Failure to achieve a PR with chemotherapy for the current relapse in previously responsive tumours; 1° Resistant = Primary resistant disease: Failure to achieve a PR with any chemotherapy used in the past; PD = Progressive Disease; NC = No Change; [c] = Response/Toxicity continues at the time manuscript submitted.
CB = chlorambucil; ChIVPP = chlorambucil, vinblastine, procarbazine, prednisolone; CHOP = cyclophosphamide, vincristine, prednisolone, doxorubicin; CVP = cyclophosphamide, vincristine, P = prednisolone; EPIC = etoposide, iphosphamide, cisplatin, prednisolone; ESHAP = etoposide, methylprednisolone, ara-c, cisplatin; EVAP = etoposide, vinblastine, doxorubicin, prednisolone; HDME + ABMT = high dose melphalan + etoposide + autograft; HICOM = high dose methotrexate, high dose ara-c, vincristine, cyclophosphamide; ImMVP16 = Iphosphamide, methotrexate, etoposide; LOPP = chlorambucil, vincristine, procarbazine, prednisolone; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; M-BACOD = methotrexate, bleomycin, doxorubicin, vincristine, dexamethasone; MP = methylprednisolone; PLAT-ETOP = cisplatin, etoposide; P = prednisolone; PROMACE-CYTABOM = doxorubicin, cyclophosphamide, etoposide, vincristine, methotrexate, bleomycin, ara-c, prednisolone; RT = involved field radiotherapy; VAPEC-B; (V) C-VAMP = (verapamil) cyclophosphamide, infusional vincristine + doxorubicin, methylprednisolone.

Table I. Treatment was offered on compassionate grounds and patients gave informed consent.

Synthesis and purification

The methodology for 2CDA was based on the condensation of 2,6-dichloropurine and 2-deoxy-3,5-bis-O-(4-methylbenzoyl)-α-D erythropentofuanosyl chloride under solid liquid phase transfer conditions. This methodology enables more efficient and safer synthesis and is suitable for large scale production (Seela & Boureois, 1989; Soula, 1985).

The drug was supplied as a sterile solution at a concentration of 2 mg ml^{-1} in 0.9% NaCl.

Drug administration

The required amount of 2CDA was added to 500 ml 0.9% NaCl and infused via a 0.2 μm filter intravenously over 24 h. This was repeated daily for 7 days. Courses were given in 28 day cycles.

Response evaluation

Disease was evaluated according to the WHO guidelines (Miller *et al.*, 1981) and assessment included CT scanning, ultrasound and a bone marrow aspirate and trephine. Patients received further courses (to a maximum of four) if there was evidence of at least a partial response. The starting dose was 0.1 mg/kg/day over 7 days and this was increased to 0.15 mg/kg/day over 7 days if the platelet and white blood cell count were respectively $> 100{,}000 \times 10^9\,l^{-1}$ and $> 1000 \times 10^9\,l^{-1}$.

Toxicity monitoring

Toxicity was recorded according to the WHO criteria (Miller *et al.*, 1981) and toxicities are shown in Table I. A full blood count was measured at least weekly between courses.

Results

Twenty-one patients received a total of 41 courses of 2CDA.

Responses

Responses are recorded in Table I and summarised in Table II.

Duration of response Eleven patients responded to treatment with 2CDA. The median duration of response is 6 months (range; 1 to 12 months). Two of the three patients who attained CR remain disease free after 12 months. One patient died in PR 8 months after treatment with no evidence of progressive disease and one patient in PR died of a neutropenic sepsis. The patient with Hodgkin's disease relapsed 6 months after treatment. The one case of lymphoblastic NHL (second relapse) attained a partial response which endured over three cycles of treatment.

Treatment failures Ten patients had no response to treatment. One patient had a low grade NHL which had responded to the first course of 2CDA but transformed to an intermediate grade NHL during a second course. Four out of six patients with transformed NHL failed to respond. Three patients with lymphoplasmacytoid lymphomas failed to respond. All three had been extensively pre treated including treatment with fludarabine. This drug has a similar mechanism of action to 2CDA and all three had failed to respond to this agent. Similarly, two patients with follicular low grade NHL, one of which secreted a paraprotein, had both received fludarabine and failed to respond. Six out of seven patients with poor performance status (WHO 2–4) failed to respond.

Toxicity The primary toxicity was myelosuppression with both leucopenia and thrombocytopenia (Tables I and III). As a result of dose limiting myelotoxicity a dose escalation (to 0.15 mg/kg/day over 7 days) was made on only three occasions. Three patients had thrombophlebitis. The five patients who had bone marrow failure prior to treatment could not be evaluated for myelotoxicity. Three patients were not evaluable for toxicity either due to death or the implementation of further treatment. All four patients who had bone marrow involvement and who were evaluable for toxicity have had continuing myelosuppression (WHO grade 1–2 thrombocytopenia; WHO grade 1–3 leucopenia) up to 8 months after treatment (Table I).

Discussion

In this series of patients it has been shown that 2CDA (0.1 mg/kg/day over 7 days (has significant anti tumour activity in pre-treated low grade NHL and in the one case of Hodgkin's disease studied. The group of patients in whom 2CDA was ineffective comprised those with lymphoplasmacytoid and transformed lymphomas, and/or poor performance status. The lack of response of the lymphoplasmacytoid lymphomas may in part be due to their previous treatment. These patients plus another patient with follicular low grade NHL had all previously failed to respond to fludarabine.

Table II Response to 2-chlorodeoxyadenosine

	Relapse			*Resistant relapse*			*Primary resistant*		
	CR	*PR*	*NC/PD*	*CR*	*PR*	*NC/PD*	*CR*	*PR*	*NC/PD*
Low grade	2	1		1	2				2
Intermediate grade		1				1			
Transformed NHL				2	4				
Hodgkin's lymphoma					1				
Lymphoplasmacytoid									3
Lymphoblastic		1							

Table III Maximum myelotoxicity of 2CDA (13 evaluable patients)

		WHO grade		
		0	*1–2*	*3–4*
Patients with BM involvement = 9	Leucopenia		2 (22%)	7 (78%)
	Thrombocytopenia		5 (55%)	4 (45%)
Patients with normal BM = 4	Leucopenia	2 (40%)	2 (40%)	1 (20%)
	Thrombocytopenia	1 (20%)	3 (60%)	1 (20%)

Fludarabine has a similar mechanism of action to 2CDA and requires phosphorylation by deoxycytidine kinase to F-ara-ATP for activation (Plunket *et al.*, 1990) and is associated with the induction of apoptosis (Robertson *et al.*, 1991). Fludarabine has been reported to have a higher ID_{50} than 2CDA against a number of cell lines indicating it may be a less active drug (Carson *et al.*, 1980). Therefore lymphoplasmacytoid tumours may be relatively resistant to 2CDA (and fludarabine). Currently we are investigating the possibility that resistance in this group of malignancies is related to a low level of deoxycytidine kinase expression.

In accord with other studies toxicity was chiefly limited to thrombocytopenia and leucopenia. One case of fatal neutropenic sepsis occurred within 28 days as receiving 2CDA. This occurred in a patient with an aggressive transformed non-Hodgkin's lymphoma associated with extensive bone marrow infiltration and bone marrow failure. He had had a partial response to one course of 2CDA. Of the patients evaluable for toxicity, four had histologically detectable bone marrow infiltration and have had continuing myelosuppression up to seven months after treatment with three courses of 2CDA.

Whatever its mechanism of action, 2CDA has a marked impact on the myeloid compartment and this has led one group to propose that it may have a role as a conditioning regimen in the setting of allogeneic bone marrow transplantation in acute leukaemia (Santana *et al.*, 1991).

The optimum dosing and dose schedule has probably not yet been reached. A regimen based on continuous infusion may not be necessary since pharmacokinetic studies have shown that after a daily 2 h infusion of 2CDA (0.14 mg kg^{-1} times 5 days), the terminal elimination phase is prolonged with a plasma half-life of 6 h and a similar area under the concentration *vs* time curve when compared to a continuous intravenous infusion schedule (Liliemark & Juliusson, 1991, Liliemark & Juliusson, 1992). Furthermore, the T/2 of 2CDA and its phosphorylated metabolites in leukaemia cells from patients with CLL and HCL is approximately 24 h, and similar for both intermittent and continuous schedules (Liliemark & Juliusson, 1992). However different conditions may apply in different tumour types as *in vitro* studies have demonstrated rapid clearance of 2CDA and its metabolites from lymphoid and myeloid cell lines (Avery *et al.*, 1989).

Oral administration of 2CDA is feasible, with a bioavailability of 20–70%, and is therefore potentially major therapeutic significance (Liliemark & Juliusson, 1992).

A partial response was attained in the one case of Hodgkin's disease studied and therefore 2CDA merits further investigation in this malignancy.

2CDA is associated with minimal non myelosuppressive toxicity and is active in extensively pre treated low grade NHL. Therefore, either singly or in combination, it represents a novel option as a salvage therapy and merits evaluation as a front line agent in this tumour.

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