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Treatment of cytomegalovirus retinitis with zidovudine and ganciclovir in patients with AIDS: outcome and toxicity

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Abstract

Sixteen patients with the Acquired Immunodeficiency Syndrome (AIDS) and cytomegalovirus retinitis were treated with ganciclovir alone (9 patients) or ganciclovir and zidovudine (6 patients). The duration of effective treatment, that is the number of weeks during which there was no deterioration in visual symptoms or retinal appearance, was comparable in both groups. However, six of the seven patients receiving concurrent therapy had to cease treatment temporarily because of bone marrow toxicity compared with one of the nine patients treated with ganciclovir alone. It is concluded that continuous concurrent therapy with oral zidovudine and intravenous ganciclovir is not possible unless unlimited supportive therapy including blood transfusion, is available.

Cytomegalovirus (CMV) is the commonest cause of retinitis in patients with the acquired immunodeficiency syndrome (AIDS) with a reported incidence of 6–30%.[1–7] Ganciclovir (9 [1, 3-dihydroxy-2-propoxymethyl] guanine) is an acyclic nucleoside which is effective in slowing the progression of CMV retinitis in AIDS patients;[8–13] however, this drug requires life long intravenous administration and its main toxicity is bone marrow depression. The antiviral drug zuidovudine has also been reported to produce regression of CMV retinitis by a hitherto unexplained mechanism.[14,15] This suggested that treatment of CMV retinitis with both zidovudine and ganciclovir might be synergistic; however, these drugs had rarely been used concurrently because of their common bone marrow toxicity. We report the results of such treatment in seven patients with AIDS and CMV retinitis and compare them with the results in nine patients treated with ganciclovir alone.

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Patients and methods

Sixteen homosexual males, aged 27–47 years (mean 36·4) with AIDS were studied. Each patient presented with symptoms of visual impairment and was referred for an ophthalmic opinion and retinal photography.

The diagnosis of CMV retinitis was made by one of us (RM) on the basis of typical fundoscopic appearances of (1) periphlebitis (2) perivascular haemorrhages and exudates.

Each patient was treated with ganciclovir at an initial dose of 7·5 mg/kg/day for 21 days, followed by maintenance therapy of 2·5 mg/kg/day. Treatment was given daily via an indwelling Hickman catheter and increased by 2·5 mg/kg/day if visual deterioration occurred. The treatment regime for zidovudine was 200 mg four hourly.

All the patients were monitored for toxicity by having weekly full blood counts and differential white cell counts, and ophthalmic examination. Changes in visual symptoms or retinal appearance were noted weekly. Treatment was considered effective for any week when visual symptoms and retinal appearances remained stable or improved.

Blood transfusions were given if the haemoglobin was below 8 gm/dl. Unacceptable bone marrow toxicity was defined as (1) more than 4 units of blood transfusion required within 14 days to maintain haemoglobin above 8 gm/dl (2) a total white cell count $< 1 \times 10^9$/l. If bone marrow toxicity occurred then treatment with zidovudine (if patient on both drugs) or ganciclovir was stopped until the haemoglobin and/or white cell count had remained above these levels for 14 days (without blood transfusion).

Table 1 Clinical details and drug efficacy

Treatment with A) ganciclovir B) ganciclovir and zidovudine	*Patient no*	*Age (yrs)*	*Additional pathology*	*Drug effective (weeks)*	*↑ maintenance therapy to 5 mg/kg/day (weeks)*
A	1	27	B cell lymphoma	2	—
	2	29	Kaposi's sarcoma	20	—
	3	31	Kaposi's sarcoma	8	—
	4	31	PCP*, sclerosing cholangitis	22	4
	5	36	Kaposi's sarcoma	16	4
	6	40	Kaposi's sarcoma	17	—
	7	41	HIV encephalopathy	41	—
	8	41	Kaposi's sarcoma	2	—
	9	42	Kaposi's sarcoma	20	—
B	1	32	PCP*	12	—
	2	33	HIV encephalopathy	20	—
	3	34	Kaposi's sarcoma	17	—
	4	37	—	41	5
	5	39	—	3	—
	6	40	—	36	4
	7	47	Kaposi's sarcoma	17	—

*PCP—*pneumocystis carinii* pneumonia.

Results

All the patients reported some improvement in their symptoms when treatment was commenced and this was confirmed on retinal examination. Nine patients were treated with ganciclovir alone and seven patients were treated with concurrent ganciclovir and zidovudine, the clinical details and outcome are shown in table 1. There was no significant difference between the two groups in terms of age, duration HIV antibody positive prior to developing CMV retinitis, or initial haemoglobin and white cell counts. Both regimes were equally effective in terms of the weeks for which visual symptoms and retinal appearances were stable. The haematological parameters of both groups are shown in table 2. There were greater transfusion requirements in patients on concurrent treatment with ganciclovir and zidovudine than in those on ganciclovir alone ($p < 0.05$, Fisher's exact test) such that treatment with zidovudine was temporarily stopped in six of the seven patients on both drugs. The relative risk of treatment withdrawal on concurrent therapy, because of toxicity was 7·5 (95% confidence interval 1·14 to 49·26).[16]

Discussion

Cytomegalovirus retinitis has a poor prognosis in patients with AIDS and prior to the development of ganciclovir there was no available therapy. This drug inhibits CMV replication in vitro, and in vivo has been reported as successful in the treatment of various forms of CMV infection including retinitis.[8 13] The major drawbacks of this treatment are the need for long term intravenous maintenance therapy and the toxic effect on the bone marrow.

At the time of this study, the antiviral agent zidovudine had been shown to prolong survival and decrease the frequency of opportunistic infections in

Table 2 Haematological effects of treatment with ganciclovir and zidovudine and resultant supportive therapy required

	Patient no	*Initial/nadir Hb g/dl*	*Initial/nadir WCC (neutrophils) × 10⁹/l*	*Initial/nadir platelets × 10⁹/l*	*Change in treatment and/or supportive therapy required*
A*	1	10·0/7·2	2·7 (1·6)/1·9 (1·5)	176/159	Blood transfusion × 4 units
	2	9·2/6·6	1·7 (1·2)/0·8 (0·35)	188/89	Bone marrow failure ? cause ganciclovir stopped
	3	10·0/7·0	2·8 (1·3)/1·2 (0·9)	150/110	—
	4	10·3/8·0	3·5 (2·5)/2·6 (2·1)	114/97	Blood transfusion × 3 units
	5	12·4/8·4	4·9 (3·8)/2·1 (1·4)	200/163	—
	6	8·9/8·4	3·3 (2·4)/1·5 (0·8)	141/137	—
	7	12·9/10·0	6·8 (3·8)/3·6 (2·0)	138/111	—
	8	12·9/8·0	1·8 (1·5)/1·4 (0·8)	153/114	Blood transfusion × 4 units
	9	8·7/7·8	2·7 (1·6)/1·9 (1·5)	97/84	Blood transfusion × 4 units
B*	1	11·2/8·0	1·89 (1·4)/1·7 (1·0)	127/73	zidovudine stopped because of anaemia. Blood transfusion × 16 units
	2	11·8/10·1	2·4 (1·2)/1·1 (0·5)	107/91	—
	3	11·6/7·5	4·1 (3·8)/2·4 (1·3)	112/82	zidovudine stopped because of anaemia. Blood transfusion × 8 units
	4	8·6/6·2	1·4 (1·0)/0·8 (0·6)	112/43	zidovudine and ganciclovir stopped because of anaemia and ↑WCC. Blood transfusion × 8 units
	5	12·4/8·0	4·9 (3·2)/2·0 (0·9)	132/62	zidovudine stopped because of anaemia. Blood transfusion × 8 units
	6	11·7/8·1	2·0 (1·9)/1·2 (1·0)	115/75	zidovudine stopped because of low WCC
	7	10·1/8·5	3·9 (2·3)/1·0 (0·6)	109/77	Blood transfusion × 8 units zidovudine stopped because of low WCC

*Treatment with (A) ganciclovir (B) glanciclovir and zidovudine.

patients with AIDS and ARC.[17] These effects may be due to an immunomodulating effect of zidovudine, although documented changes in CD_4, numbers have been transient.[17] There have been reports of regression of CMV retinitis in AIDS patients treated with this drug which has no direct anti CMV effect.[14,15] This may be comparable with the regression in CMV retinitis which occurs on reversal of transient immunodeficiency states.[18] Another explanation, as suggested by Skolnick, might be that infection with HIV and CMV increases replication of both viruses and hence inhibition of either would slow down progression of both.[19] It would seem likely in view of these findings that concurrent therapy with ganciclovir and zidovudine would be advantageous in AIDS patients with CMV retinitis, but they have rarely been given in this way because of their shared toxicity to the bone marrow. One report of such treatment found it possible to use the drugs concurrently but gave unlimited transfusion (average 2·4 units per patient) and reduced treatment on the basis of granulocytopenia alone.[20] In this study the patients were given ganciclovir 5 mg/kg/day for five or seven days per week as maintenance therapy. At the time of our study the recommended dose of maintenance therapy for ganciclovir was 2·5 mg/kg/day and despite this we had considerable tranfusion requirements, such that zidovudine treatment was withdrawn temporarily in six of the seven patients. We found no evidence of synergism in terms of duration of retinal stabilisation, but as zidovudine was stopped in so many cases synergy was not adequately assessed.

Many of our patients had abnormal haematological parameters prior to ganciclovir treatment which may have contributed to the cytopenias which developed in many, and other forms of therapy should be considered in this situation. Foscarnet is an alternative anti-CMV agent which has little haematological toxicity and may be combined with zidovudine therapy; however it may produce electrolyte disturbances and nephrotoxicity and is administered over a prolonged period.[21]

We consider that the toxic effects of concurrent therapy with ganciclovir and zidovudine are unacceptable and we suggest that the use of alternative methods of drug delivery should be further explored. Intravitreal injections of ganciclovir and the newer anti CMV agent foscarnet have been reported to meet with some success.[22-24] Concurrent therapy with zidovudine and intravitreal anti CMV therapy might produce synergistic effects without the considerable toxicity we have encountered.

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