High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's disease

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Abstract

We treated five patients with intractable sympathetic ophthalmia and six patients with severe Behçet's disease by high-dose, short-term chlorambucil therapy. We used a total dose ranging from 306 mg to 4.2 g and a duration of therapy no longer than 36 weeks and in most cases less than 24 weeks. After termination of therapy all 11 patients had a sustained remission of their eye disease. Unless subretinal neovascularisation was present, all had a final visual acuity of 20/50 or better. Malignancy has not developed in any of our cases, with a follow-up ranging from 6 months to 12 years (mean, 4.5 years). Although 30- and 40-year follow-ups and larger numbers of patients may be necessary fully to realise the risks of chlorambucil, we believe that our high-dose, short-term regimen (Behçet's disease: average duration, 23 weeks; average total dose 2.2 g; sympathetic ophthalmia: average duration, 11 weeks; total average dose, 0.9 g) may be safer than previously reported chlorambucil regimens of one to two years or longer. In addition we fulfilled our aim of discontinuing all concomitant systemic corticosteroids within a relatively short time (usually six to eight weeks).

Since the early 1970s¹⁻⁴ chlorambucil has been reported to be effective in the treatment of both Behçet's disease and sympathetic ophthalmia (SO). Dosage and length of therapy have varied, and many reports have questioned its safety as an immunosuppressive agent.⁵⁻¹¹

We attempted to establish a chlorambucil regimen that would be effective and have minimal risks. We herein describe five patients with intractable sympathetic ophthalmia and six patients with severe Behçet's disease who were successfully treated with one-time, short-term, high-dose chlorambucil therapy. We emphasise the importance of this dosage schedule and contrast the results of high-dose, short-term (approximately 6-month) treatment with those of other studies using lower-dose, long-term therapy.¹⁻⁴ After the termination of therapy all our patients had a sustained remission of their eye disease. Follow-up ranged from six months to 12 years, with a mean of 4.5 years.

Patients and methods

PATIENTS

The diagnosis of Behçet's disease and SO were made by standard clinical criteria.^{12,13} In patients with SO, if there was no potentially useful vision in the exciting eye, such as visual acuity of hand

motions or worse, coupled with irreparable retinal detachments or severe anterior chamber derangement, enucleation was recommended. Patients were considered for chlorambucil therapy if they were only partially responsive to high-dose oral corticosteroids or if they had suffered serious side effects of corticosteroids such as diabetes mellitus, uncontrolled glaucoma, or psychological problems. Patients and, when available, their families were told the side effects of chlorambucil along with its potential benefits. Stressed potential side effects included late malignancy and sterility. Patients were not allowed to make an instantaneous decision, and most took one or more weeks to decide about therapy. An informed consent form was signed by all patients or their parents.

Patients without active inflammation and patients with macular scars and/or optic nerve atrophy were not given chlorambucil, because little visual improvement could be expected from immunosuppressive therapy.

METHODS

Treatment was similar to the regimen described by Godfrey *et al.*² Dosing was begun at 2 mg (1 tablet) daily. This low dose provides a margin of safety for an idiosyncratic acute bone marrow depression. In the absence of a white blood cell (WBC) count below $2.4 \times 10^9/l$ or a platelet count below $100 \times 10^9/l$ the dosage of chlorambucil was increased by 2 mg/day each week. This weekly increase was maintained unless the WBC or platelet parameters were reached or unless there was clinical remission of minimal, low-grade inflammation (trace to 1+ flare or rare, occasional cells) with no active fundus lesions present. If the blood count parameters were reached, the chlorambucil therapy was abruptly terminated.

All patients were receiving oral prednisone at the time of institution of chlorambucil therapy. As they showed a stable or improving clinical response with the increasing chlorambucil dosage, the prednisone dosage was tapered. The goal was to treat the patients with chlorambucil alone without concomitant prednisone therapy. This goal was accomplished slowly, over six to eight weeks.

In all but two cases, when prednisone therapy was entirely discontinued, the chlorambucil dose was increased to compensate for the loss of the anti-inflammatory effects of prednisone. Once low-grade inflammation was achieved, an attempt was made to continue chlorambucil therapy at the same dosage without concomitant prednisone for three months. However, in all but one case the blood cell count dropped to a level described above as too low to achieve a three-

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month goal. In two cases, when chlorambucil was being used alone, the WBC or platelet counts appeared to be approaching the cut-off levels stated above, the dosage was decreased by 2 to 4 mg daily. In the other cases the dosage was maintained if the disease was stable or steadily increased if the disease was active. After three months of therapy at levels of minimal ocular inflammation or if the WBC level fell below $2.4 \times 10^9/l$ or the platelet count fell below $100 \times 10^9/l$, chlorambucil therapy was abruptly discontinued. Blood cell counts were followed weekly.

No attempt was made to measure dose by body weight or mass. Patients were given only enough chlorambucil for one week of therapy to guard against their non-compliance.

Results

Twenty-three and 22 patients were diagnosed as having SO and Behçet's disease respectively in the period from 1973 to 1988. Six of 23 patients diagnosed as having SO were treated with chlorambucil. One of the six patients was not included in the series because the chlorambucil was not administered by us or by our dose techniques. The 17 patients not treated with chlorambucil had disease amenable to control with topical, periocular, or systemic corticosteroids. Thus we include five patients with SO in the report.

Six of 22 patients diagnosed as having Behçet's disease were treated with chlorambucil. One patient declined chlorambucil after the side effects were explained. Three patients were thought to have irreparable damage to the retina and were not offered therapy. Twelve patients appeared to have mild ocular disease easily controlled with topical and low-dose short-term prednisone therapy.

Figure 1 shows the distribution of follow-up for patients with SO and Behçet's disease.

When WBC or platelet counts fell to the cutoff levels of $2.4 \times 10^9/l$ or $110 \times 10^9/l$ respectively, these counts usually recovered to normal levels in about six weeks. Once the patients went through this six-week depression, they invariably had a sustained remission with no active inflammation. If the WBC or platelet counts recovered to normal levels sooner (one to three

Figure 1: Distribution of follow-up in patients with Behçet's disease and sympathetic ophthalmia.

weeks), a second short course of chlorambucil would be required to lower the counts again to achieve that six-week depression period. One patient's counts returned to normal within two weeks when a $2.8 \times 10^9/l$ WBC count was used as the cut-off to discontinue chlorambucil treatment. When we lowered the WBC cut-off to $2.4 \times 10^9/l$, her WBC counts decreased to low levels ($0.9 \times 10^9/l$ to $1.6 \times 10^9/l$) and slowly recovered over six weeks. Only then did her disease go into sustained remission.

As seen in Table I, no patient had over 36 weeks of treatment. All patients but two, patients 3 and 6, had less than six months of therapy with chlorambucil. The total dose ranged from 306 mg to 4.2 g.

There were notable differences in total dose and duration of therapy when comparing the patients with Behçet's disease and those with SO. The former group received a mean dose of 2.18 (SD 1.10 g, range 1.29 to 4.20 g). The SO group received a mean dose of 0.85 (SD 0.48 g, range 0.31 to 1.53 g; $p=0.03$ by Student's *t* test). The duration of chlorambucil therapy was 22.8 weeks (SD 9.0, range 14 to 36 weeks) for the Behçet's group and 11.2 weeks (SD 3.2, range 7 to 15 weeks) for the SO group ($p=0.02$, Student's *t* test). The patients' highest daily dosage ranged from 10 to 28 mg. After patient 11 took 92 mg in a single dose during a suicide attempt she recovered and went into sustained complete remission.

Visual acuities before and after chlorambucil therapy are shown in Figure 2. Final visual acuities in the patients with Behçet's disease were all 20/50 or better. Four of the 12 eyes with Behçet's disease had a final visual acuity of 20/20, and seven of the 12 eyes had a post-treatment

TABLE I Clinical characteristics of patients receiving chlorambucil

Patient no./ age (yr)/sex/ race	Initial VA		VA just before chlorambucil therapy		Final VA		Follow- up (yr)	Highest dosage (mg/day)	Total dose (mg)	Duration of therapy (weeks)
	OS	OD	OS	OD	OS	OD				
Behçet's disease*										
1/15/M/Ind	20/80	20/80	20/50	20/60	20/40	20/25	1	20	1288	14
2/17/F/W	HM	20/30	3/200	20/200	20/50	20/20	12	22	1540	25
3/28/F/W	20/20	20/60	20/30	20/200	20/20	20/30	1	24	2688	30
4/26/F/W	20/25	HM	20/25	20/60	20/20	20/40	5	24	1582	15
5/38/F/W	20/30	20/20	3/160	1/200	20/25	20/30	3	22	1750	17
6/26/M/B	20/70	20/400	20/300	20/200	20/25	20/20	7	28	4200	36
Sympathetic ophthalmia										
7/6/F/W	LP	20/25	Enuc	20/40	Enuc	20/25	9	10	490	9
8/25/F/H	Enuc	20/40	Enuc	20/40	Enuc	20/20	2	14	868	12
9/54/M/W	CF	20/400	CF	20/400	4/200+	20/200+	3	18	1064	15
10/42/M/B	20/25	LP	20/50	Enuc	20/20	Enuc	1-2	22	1526	14
11/16/F/Ind	NLP	8/400	NLP	8/400	NLP†	20/200+	3	92‡	306	7

VA indicates visual acuity; Ind, Eastern Indian; W, white; B, black; H, Hispanic; HM, hand motions; LP, light perception; Enuc, enucleated; CF, counting fingers; and NLP, no light perception.

*All patients had complete Behçet's disease except patient 1; †Subretinal neovascularisation was present; ‡Suicide attempt.

Our finding that patients obtained sustained remission when the WBC or platelet levels remained depressed for about six weeks suggests a need to induce this toxic response. If we were to increase the dose of chlorambucil more rapidly, perhaps the total dose and duration of therapy might be further decreased and fewer side effects might occur. The paucity of patients with SO and Behçet's disease who qualify for this therapy

makes it necessary to have collaborative trials of randomised drug regimens.

Because chlorambucil is an immunosuppressive agent, a substantial number of viral, bacterial, and fungal infections as well as a 2% incidence of septicaemia and death have been reported in patients with rheumatoid arthritis treated with it long term.³² Others have also reported infections accompanying long-term chlorambucil therapy.^{3,29} Our patients have experienced no secondary infections while receiving chlorambucil.

Chlorambucil has also been reported to depress sperm counts and to inhibit the development of male secondary sexual characteristics.^{10,11,33-36} Total chlorambucil doses less than 7.0 to 8.2 mg/kg in children^{11,33} and 400 mg³⁴ of 6.1 mg/kg³⁵ in adults are believed not to affect fertility. Recovery of spermatogenesis has been noted by some³⁶ but not all investigators.^{10,11}

The potential problem of male sterility makes it crucial to obtain informed consent. We inform our male patients of these findings and suggest to those who want children that they have sperm placed in a sperm bank in case they are sterilised by the drug. One 17-year-old patient in our series chose to place his sperm in a bank before beginning chlorambucil therapy. Artificial insemination after cryopreservation of semen in men with testicular tumours or Hodgkin's disease has been reported to result in a pregnancy rate of 45% at six months, compared with a usual cumulative probability of pregnancy of 71%.³⁷ One pregnancy occurred from semen that had been stored for 6.5 years.³⁷ We have no follow-up on the actual fertility of our male patients.

Little has been written about the effect of chlorambucil on women. Girls and women treated with chlorambucil for renal disease and malignancy have had normal children and normal levels of oestradiol, follicle stimulating hormone, and lutenising hormone,^{33,38} though chlorambucil in combination with other chemotherapeutic agents can cause gross histological disruption of the ovaries and amenorrhoea.^{39,40} Care must be taken that patients are not or do not become pregnant during therapy because of the possibility of teratogenic effects.^{41,42} One of our patients who became pregnant after terminating chlorambucil therapy had a normal delivery and child.

Other serious side effects of chlorambucil are rare and usually occur after long-term therapy (over several years) with multiple dose regimens. These side effects include myelofibrosis,⁴³ bone marrow failure,⁴⁴ rashes,⁴⁵ and pulmonary fibrosis.⁴⁶ None of our patients has experienced these side effects.

For the previously stated reasons, chlorambucil should be used only in those patients for whom blindness is a real possibility without therapy. Prolonged follow-up may be necessary to understand fully the risks of chlorambucil.

Despite potential side effects chlorambucil has several advantages over other agents that might be used to treat SO or Behçet's disease. Cyclophosphamide, an alkylating agent closely related to chlorambucil, is also used to treat non-malignant inflammatory diseases such as Wegener's granulomatosis and nephritis.

However, because of its more rapid action, cyclophosphamide may be a more difficult drug to administer than chlorambucil,^{18,47} and toxic effects may occur more rapidly than with chlorambucil. Sister chromatid exchange, a sign of chromosome damage, is greater with cyclophosphamide than chlorambucil.⁴⁸ Cyclophosphamide is also a teratogenic agent.⁴⁹ Furthermore, cyclophosphamide can cause male and female sterility,⁴⁹ haemorrhagic cystitis,⁴⁹ and bladder carcinoma,⁵⁰ possibly due to renal excretion of active metabolites.^{49,51} Patients receiving cyclophosphamide require vigorous hydration to limit the bladder damage. Cystitis and bladder cancer are not associated with chlorambucil therapy.

Cyclosporin, a newer immunosuppressive agent, has been recently used to treat uveitis.⁵²⁻⁵⁴ In one study nine patients with refractory posterior uveitis were given systemic cyclosporin. All patients had an improved visual acuity, a reduced corticosteroid dose, and decreased inflammation. However, in seven patients, cyclosporin-induced renal toxicity necessitated a reduction in dose, which led to a relapse of the uveitis.⁵² Other reports indicated a need to taper the cyclosporin dose because of nephrotoxicity and to add systemic corticosteroids to the regimen to suppress inflammation.⁵⁴ A recent monograph emphasises the frequent need to use corticosteroids with low-dose cyclosporin.⁵⁵ Relapses of cases of Behçet's disease after discontinuing cyclosporin are reported.⁵⁶ These results indicate that cyclosporin suppresses inflammation but does not cause a long-term remission. Terminating cyclosporin therapy frequently results in rebound inflammation.⁵⁷ This is in contradistinction to the results with our regimen of chlorambucil, in which terminating chlorambucil therapy when toxicity was reached resulted in sustained remission of inflammation. Patients with severe uveitis appear to need long-term cyclosporin therapy, which has been associated with renal toxicity⁵⁷ and lymphoma.⁵⁸ Our experience with chlorambucil has necessitated only short-term therapy.

In summary, we have found chlorambucil to be useful in selected cases of SO and Behçet's disease. By using a technique of high-dose short-term therapy we could discontinue the use of systemic corticosteroids, place our patients into sustained remission, and theoretically reduce the side effects of chlorambucil. Thus we achieved our aim of eliminating side effects of long-term corticosteroids in addition to discontinuing all systemic medications within a relatively short period.

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