Chlorambucil

23

Howard H. Tessler

Contents

Core Messages

- Chlorambucil is a powerful and potentially dangerous drug that can be used to treat patients with severe uveitis in which other treatments have failed.
- Chlorambucil like cyclophosphamide, the other commonly used alkylating agent, can place patients is sustained remission of their chronic disease such that they no longer require medication.

23.1 Mechanism of Action and Pharmacokinetics

Chlorambucil (*Leukeran*) is an alkylating agent that has been available since 1952. Alkylating agents substitute an alkyl group for hydrogen ions in organic compounds. Alkylation of DNA results in binding of DNA strands so they cannot "unzip" and replicate. Cell death is induced in rapidly proliferating tissue such as the bone marrow. Chlorambucil is readily and reliably absorbed orally with availability of 56–105 %. Bioavailability increases from 50 to 75 % when taken on a full stomach. The half-life in the serum is 1.5 h, and it is metabolized in the liver to phenyl acetic acid mustard which also has cytotoxicity. Hydrolysis of both chlorambucil and phenyl acetic acid mustard to inactive compounds results in elimination of less than 1 % of

H.H. Tessler, MD
Professor Emeritus of Ophthalmology, University of Illinois at Chicago, 48 S Greenleaf, Gurnee, IL, 60031, USA
e-mail: howatess@uic.edu

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both in the urine. Chlorambucil has a very slow onset of action (~4 weeks for full activity) making acute toxicity unlikely [8, 9, 13].

The standard dose is 0.1–0.2 mg/day. The tablet is 2 mg in size. This comes to 4–12 mg/day for the average patient. The entire dose may be taken at once preferably on a full stomach. *A weekly CBC including platelets is necessary* [13].

23.2 Side Effects

Opportunistic infections such as herpes zoster may occur while chlorambucil is taken. Nausea is uncommon below 20 mg/day. As opposed to cyclophosphamide, alopecia and bladder toxicity do not occur.

Hematologic

Bone marrow suppression is the primary side effect of chlorambucil. Typically this suppression is reversible, but it may be prolonged. On rare occasions, bone marrow aplasia may occur.

Late Malignancy

This is the most worrisome potential complication of alkylating agents when used to treat autoimmune disease. The risk of late malignancy with alkylating agents appears to be greater than with other forms of immunosuppression [10, 17]. The analysis of sister chromatid exchanges (SCE) is a cytogenetic technique use to show DNA damage as a result of an exchange of DNA between sister chromatids. An increase in SCE is seen with chlorambucil. Damage is related to daily dose and duration. It is believed that chromosome damage is related to risk of malignancy [25]. Chromosome damage may persist for years after discontinuing chlorambucil [27].

In a randomized controlled trial of 431 patients seen from 1967 to 1974 for the treatment of polycythemia vera, the rate of acute leukemia in chlorambucil treated patients was 2.3 times the rate in patients given radioactive phosphorus and 13 times the rate in patients treated with phlebotomy alone [5]. Three to fourteen percent of patients treated with traditional long-term chlorambucil for rheumatoid arthritis developed leukemia or lymphoma [20]. Thirty-nine patients with rheumatoid arthritis treated with chlorambucil were compared with 30 patients treated with azathioprine or 6-mercaptopurine. A mean daily dose of chlorambucil of 4.25 mg was given with a mean duration of 25 months. Eight patients treated with chlorambucil developed cutaneous malignancy as opposed to 1 treated with the other agents ($p=0.03$). Three patients of the 39 treated with chlorambucil developed leukemia or a preleukemic state, while none of the patients treated with the purine analogues did [26]. The risk of malignancy is related both to the total cumulative dose and total duration of therapy [21, 34]. Among 1,711 patients followed for 1–13 years, no cases were seen in patients treated for less than 6 months or with less than 1 g of chlorambucil [19].

Reproductive

Permanent sterility usually occurs in men, while amenorrhea occurs in women [30]. Women younger than 20 usually will regain menses and fertility, but in older women, early onset menopause frequently occurs. Men who need chlorambucil can place sperm in a sperm bank prior to therapy. Women should be evaluated by a gynecologist and consider trying to preserve fertility with injections of gonad-releasing hormone agonistic analogue (GnRH-a) (*Lupron*). Cryopreservation of human ova is unreliable and not currently available [7]. Chlorambucil can cause fetal damage and should be avoided in pregnancy [13].

Dermatologic

Allergic reactions such as urticaria and angioneurotic edema can occur. Rare reports exist of skin rash leading to erythema multiforme [13]. This author has seen a few patients develop

Table 23.1 Drugs that may interact with chlorambucil despite manufacturer's insert states there are no drug interactions

Barbiturates: may increase conversion in liver to active metabolite
Nalidixic acid: may be contraindicated
Digoxin: may reduce adsorption

eczema while on chlorambucil when the concurrent prednisone they had been taking is discontinued.

CNS

Rarely seizures, tremors, myoclonia, confusion, ataxia, and hallucinations have been reported [13] (Table 23.1).

23.3 Experimental and Clinical Data for Uveitis

There is no published data on the use of chlorambucil in experimental uveitis.

Chlorambucil has been used to treat severe intractable uveitis since the late 1960s [23, 31]. It has been especially useful in treating sight-threatening diseases such as Behçet's disease, sympathetic ophthalmia, and serpiginous choroiditis [1, 2, 18, 22, 24]. Remission rates of 60–80 % of the uveitis for up to 2 years or more have been reported [26, 32].

There have been two approaches to the use of chlorambucil in patients with uveitis, traditional dosage (0.1–0.2 mg/kg/day) and short-term high-dose therapy.

In one study of five patients with uveitis, three (60 %) had sustained remission after one course of traditional dosage therapy. The other two patients had mild recurrences of posterior uveitis 8–10 months after cessation of chlorambucil therapy. This necessitated retreatment with oral corticosteroids and chlorambucil [32]

A report of 53 patients with ocular inflammatory disease treated with STHD chlorambucil with an average follow-up of 4 years (range 6 months to 24 years) has been reported [15]. The total cumulative dose of chlorambucil for these patients was 1,429 mg (range 392–5,200 mg). Thus, this dose exceeded the 1 g total safety limit to avoid malignancy previously referenced [19]. Nevertheless, no malignancies were noted in this group of 53 patients. Average duration of therapy for these 53 patients was 16 weeks (range 7–40 weeks). This study was updated with a mean follow-up of 8.9 years [6]. In this follow-up study, there were no cases of lymphoma or skin cancer and no increased incidence of other cancers. Only 4 of these 53 patients (8 %) had over 26 weeks of therapy. It is hypothesized that the short duration of therapy may be more important than the total dose in reducing the risk of malignancy. Forty-one of the fifty-three patients (77 %) were in remission with no recurrence of disease at follow-up. That is, these patients in remission no longer required systemic therapy. However, 16 patients still required topical medication. Diseases treated included Behçet's disease (17 patients), sympathetic ophthalmia (8 patients), scleritis (6 patients), severe iridocyclitis (6 patients), serpiginous choroiditis (5 patients), retinal vasculitis (4 patients), Vogt-Koyanagi-Harada's disease (2 patients), intermediate uveitis (1 patient), birdshot retinochoroidopathy (1 patient), multifocal choroiditis (1 patient), intraocular juvenile xanthogranuloma (1 patient), and autoimmune retinopathy (1 patient).

Side effects of therapy in this study of 53 patients included secondary amenorrhea in seven females (26 %). Two patients treated in their teens were later able to conceive normal children. One female treated at age 6 has had normal menses as an adult. Previous authors have reported normal children in young girls treated with chlorambucil for leukemia [16]. Three male patients reported sexual deficiencies.

Non-ophthalmic herpes zoster developed in 6 of 53 patients (12 %). Two patients required platelet transfusions. The patients that required platelet transfusions were treated at a time that the cutoff of chlorambucil was a platelet count of 100,000/mm^3. Since raising the cutoff level to 125,000/mm^3, no platelet transfusions have been required (Table 23.2).

23.4 Indication and Dosage

Traditional Dosage

The traditional regimen consists of a dose of 0.1–0.2 mg/kg/day (6–12 mg daily) as a single daily dose. Frequently, the white blood count (WBC) is kept to a level of 3,200–3,500/mm^3. Oral corticosteroids are tapered and discontinued as the ocular inflammation comes under control. Therapy is given for 1 year after quiescence of the disease. This prolongation of therapy is done in the hopes of providing a long-term remission off all therapy [22, 23].

Short-Term High-Dose Therapy

Short-term high-dose (STHD) therapy attempts to reduce the risk of malignancy by reducing the duration of therapy [3]. The method of therapy is a variation of the technique first described by Godfrey et al. [14]. The drug is started at a dose of 2 mg (1 tablet) daily. Weekly blood counts are obtained while patients are on chlorambucil. If the WBC is greater than 3,000/mm^3, the dose is increased by 2 mg/day each week. Thus, at week 3, the patient would be taking 3 pills daily (6 mg). If the WBC is at 3,000/mm^3, the dose is held steady, and if the WBC is at 2,800/mm^3, the dose is decreased by 2–4 mg/day. Chlorambucil is abruptly discontinued if the WBC falls below 2,400/mm^3 or if the platelet count falls below 125,000/mm^3 [15, 18]. Patients receive weekly blood counts on this regimen and are examined every 1–2 weeks. Patients who cannot cooperate with this regimen of frequent follow-ups are not allowed to continue with therapy. Patients are only given enough medication until the next visit. Systemic corticosteroids and other immunosuppressive drugs are withdrawn as chlorambucil takes effect. A goal of this STHD therapy is to have the patients only taking chlorambucil and no other systemic therapy for at least 3 months before ending therapy. Frequently, the WBC and/or platelets drop, so this 3-month course is not possible.

Relation of STHD Chlorambucil to Rebooting of the Immune System

Immunoablative treatment with cyclophosphamide does not damage hematopoietic "stem cells." This permits repopulation of the bone marrow without a bone marrow transplant. This type of therapy can induce long-lasting remission in autoimmune diseases. Three patients with myasthenia gravis treated with high-dose cyclophosphamide (50 mg/kg/day intravenously for 4 days), then placed in protective isolation until their bone marrow recovered, went into long-term remission of myasthenia for at least 3.5 years [11]. This is a milder form of autologous hematopoietic stem cell transplantation in which patients have their stem cells mobilized with cyclophosphamide (2.0 g/m^2) and undergo leukapheresis with cryopreservation of the autologous stem cells. The patients are then given cyclophosphamide at 200 mg/kg and later reinfused with their own cryopreserved stem cells [33]. This type of therapy has been used in juvenile diabetes mellitus, systemic sclerosis, rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosus [28]. It is interesting to speculate if STHD chlorambucil therapy when it works best and a patient's blood count takes about 6 weeks to recover is a mild form of this rebooting of the immune system.

Chlorambucil Compared to Other Drugs for Uveitis

Chlorambucil is a second- or third-tier therapy. Less potentially toxic therapies such as methotrexate, azathioprine, mycophenolate, and cyclosporine should be considered prior to the use of chlorambucil.

With the advent of the anti-TNF drugs, ophthalmologists have an additional but expensive potent therapy for the treatment of severe uveitis. The anti-TNF drugs are less toxic and less dangerous than the alkylating agents. Thus, for most patients, the anti-TNF drugs should be considered prior to going to an alkylating agent. However, the anti-TNF drugs do not place

Table 23.2 Design and outcome of selected studies on chlorambucil in the treatment of uveitis

Authors (year)	Type of study	Subtype of uveities	No. of pat/eyes	Previous treatment	Dosing regimen	Follow-up	Outcome	SE
Abdalla and el-D Bahoat (1973) [1]	Case control	BD	7/nr	CS	Chlorambucil 10–15 mg/day + prednisone 6–11 months	3.5 years	All CII off all systemic medication	Leucopenia Drug rash
Akpek et al. (2002) [2]	RCR	Serpiginous choroiditis	5/nr	CS	STHD chlorambucil	15–80 months	CII	Leucopenia
Benezra and Cohen (1986) [4]	RCR	BD	20/nr	CS	Chlorambucil Dose not given	Up to 25 months	16/20 CII	nr
Godfrey et al. (1974) [14]	RCR	Various	31/nr	CS	Chlorambucil 8–22 mg/day		10 improved 8 borderline 13 no change 4/5 BD improved	Leucopenia Thrombocytopenia 1 seizure
Goldstein et al. (2002) [15]	RCR	Various	53/nr	CS	Chlorambucil 10–30 mg/day 7–40 week therapy (STHD)	0.5–24 years	77 % CII	Amenorrhea Herpes zoster Thrombocytopenia No malignancies
Jennings and Tessler (1989) [18]	RCR	Sympathetic	6/nr	CS azathioprine	STHD	1–5 years	CII	Leucopenia
Mamo (1976) [22]	RCR	BD	14/nr		Chlorambucil 6–8 mg/day occasional 20 mg/day	3–66 months	13/14 CII	None reported
Tabbara (1983) [30]	RCR	BD	10/20		Chlorambucil 0.2 mg/kg		15/20 eyes 20/200 or less	Azoospermia Oligospermia

BD, Behçet's disease, *RCR* retrospective case review, *SE* side effect, *CII* controlled intraocular inflammation, *CS* corticosteroids, *nr* not reported

Table 23.3 Cost/year of various immunosuppressive drugs to treat uveitis in 2013 in the USA

Drug	Cost ($)
Methotrexate (generic)	555
Azathioprine (generic)	475
Cyclosporine (generic)	3,700
Mycophenolate	1,851
Infliximab	25,600
Adalimumab	28,320
Cyclophosphamide 1 year	2,900
High-dose short-term chlorambucil 16 weeks	2,000

patients in sustained remission as do the alkylating agents. Thus, as opposed to STHD chlorambucil therapy, patients may require the anti-TNF medication for years. The long-term risks of anti-TNF therapy still needs to be established [35].

There is a cost-benefit to the alkylating agents over anti-TNF medication (Table 23.3). In the United States, anti-TNF drugs are not approved by the FDA (Federal Drug Administration) for the use in most kinds of uveitis. Thus, private insurance companies and government insurance (Medicare) frequently refuse to pay for anti-TNF therapy. This is true in other countries besides the United State. In a patient at risk for blindness, economics may force them to an alkylating agent. Also, some patients when told of the high chance of sustained remission after alkylating agent therapy and the chance of being off all medication may prefer treatment with STHD chlorambucil to facing years of anti-TNF therapy (Table 23.3).

Cyclophosphamide is more popular than chlorambucil, possibly because bone marrow toxicity is more predictable [29]. Cyclophosphamide may be preferred over chlorambucil because of more rapid onset of action; chlorambucil can take 4 weeks to really begin working. However, if a patient has had a reaction to cyclophosphamide such as hemorrhagic cystitis, bladder cancer, or alopecia, chlorambucil may be preferred.

23.5 EBM Grading

Type IIb, suggestion for therapy: Grade A

Take-Home Pearls

- Chlorambucil therapy should be reserved for severe sight-threatening noninfectious uveitis including chronic Behçet's disease, sympathetic ophthalmia, and Vogt-Koyanagi-Harada's disease.
- It should be used when safer therapies such as methotrexate, cyclosporine, and TNF-alpha inhibitors fail or are not available.
- Short-term high-dose (STHD) therapy with chlorambucil is an effective method of placing as many as 77 % of patients with severe uveitis into long-term sustained remission.

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