CHAPTER 12

CHLORAMBUCIL

Evren Odyakmaz Demirsoy, MD.

Chlorambucil is an alkylating agent derived from nitrogen that preferentially affects both B cells and T cells. This agent is approved by FDA for chronic lymphocytic leukemia, malignant lymphoma and Hodgkin's disease.[1, 2] Potential effect of developing secondary malignancy of chlorambucil limits its usage. But, off-label use of chlorambucil in several dermatologic diseases, especially in diseases which are severe and resistant to other treatment agents, has been found safe and effective.

Chlorambucil is well tolerated and absorbed when given orally. Plasma half-life is 1.5 hours and it is metabolized by the liver. Chlorambucil and its metabolites are extensively bound to plasma and tissue proteins. In vitro, chlorambucil is 99% bound to plasma proteins, mostly to albumin.[1-3]

Chlorambucil is available in a 2 mg tablet form. The usual dosage of chlorambucil is 0.1 to 0.2 mg/kg daily for 3 to 6 weeks.

Chlorambucil is vault to D status in pregnancy.

Mechanism of action

Chlorambucil is a cell-cycle phase nonspecific alkylating agent which damages DNA via cross-linking. Chlorambucil interferes with DNA replication and induces cell apoptosis. [3]

Dermatological indications

Chronic lymphocytic leukemia, malignant lymphoma and Hodgkin's disease are the diseases that chlorambucil is approved by FDA. Efficacy of this agent in some dermatological diseases has been shown.

Chlorambucil is a systemic chemotherapy agent for mycosis fungoides but generally reserved for patients with advanced-stage Mycosis Fungoides and Sezary syndrome who have either relapsed after treatment with skin-directed therapies and biologic-response modifiers or have extensive disease with visceral organ involvement. Low-doses of chlorambucil may be used for patients with minimal disease that is slowly progressive or for elderly patients with a poor performance status.[4] Clorambucil with or without rituximab is recommended for patients with primary cutaneous marginal zone lymphoma and primary cutaneous follicle center lymphoma who have generalized skin disease.[5]

Although necrobiotic xanthogranuloma is a rarely seen disease, it is one of the diseases in which this cytotoxic agent is commonly used in dermatology. There are some case reports and case series treated successfully with chlorambucil. Ryan et al gave chlorambucil (10 mg daily for 14 days followed by a 14 day drug free interval before the next cycle for a total eight cycles) to their patients with necrobiotic xanthogranuloma associated with chronic lymphocytic leukemia. They observed significant regression of lesions in the second cycle of treatment. They noted that at the end of the therapy all lesions had healed and no recurrence had been seen in the next two years. [6] Chlorambucil has been reported as an effective agent in patients with severe pyoderma gangrenosum whose disease failed after less toxic therapies.[7, 8]

Chlorambucil had been used successfully as a steroid sparing agent in autoimmune blistering diseases. [2, 9, 10] Shah et al reported 9 patients with pemphigus (7 with Pemphigus vulgaris, 2 with pemphigus foliaceus) who were treated with chlorambucil and prednisone concurrently after having failed to respond to other immunosuppressive treatments. Chlorambucil was initially given as 4mg daily at the beginning but the dosage was increased according to therapeutic response (maximum 10 mg once daily) and side effects. Clinical improvement was observed in 6 of 9 patients. Three patients experienced cytopenia as a side effect.[2]

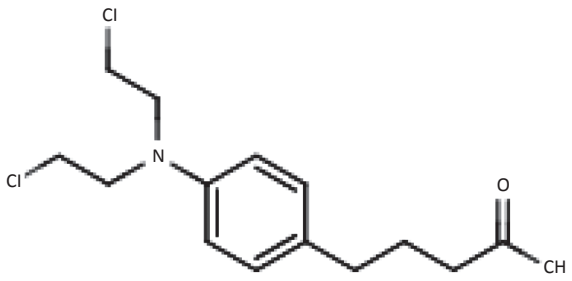


Figure 1. Chemical composition of chlorambucil

Chave et al reported their 45 patients with bullous pemphigoid who were treated with chlorambucil and/ or prednisolone. They thought, chlorambucil could be an effective and safe treatment option for bullous pemphigoid when used in conjunction with corticosteroids.[9]

In Behcet's disease, major indications of chlorambucil are uveitis and meningoencephalitis.[11-13] However, the frequency of toxicity reduces its usefulness, thus, some investigators have abandoned chlorambucil treatment for Behcet's disease.[14]

There are some reported case series and cases in which chlorambucil was shown to be effective against sarcoidosis, in 1990s and before.[15, 16] In one of the clinical studies chlorambucil therapy was given to 31 patients with severe sarcoidosis who were unresponsive or intolerant to corticosteroids. Marked or moderate improvement was achieved in 28 of 31. But 6-month course of chlorambucil was often followed by relapse highlighting the require for prolonged therapy in most patients.

Contraindications. See table 1.

TABLE 1. Indications, contraindications and side effects of chlorambucil.

FDA-approved indications	
Chronic lymphocytic leukemia	
Lymphoma	
Hodgkin's disease	
Off label uses	
Neoplastic diseases	Nonneoplastic diseases
Cutaneous T cell lymphoma[4]	Bullous pemphigoid[10]
Sezary syndrome[20]	Pemphigus vulgaris[2]
Cutaneous B cell lymphoma[5]	Wegener granulomatosis [21, 22]
	Behcet's disease[11, 13, 23-25]
	Cutaneous sarcoidosis[15, 16]
	Sweet's syndrome[26]
	Dermatomysitis [27]
Contraindications	Relative
Absolute	Active infection
Drug allergy	Renal insufficiency
Depressed bone marrow function	Seizure disorder
Pregnancy (category D)	
Lactation	
Dosage 0.1-0.2 mg/kg/day	
Side effects	
Hematologic	*Dermatologic*
Anemia	Alopecia
Leukopenia	Drug fever with lymphadenopathy
Thrombocytopenia	Drug rash with eosinophilia and systemic symptoms
Gastrointestinal	Morbiliform rash
Nausea, vomiting, diarrhea	Mucosal ulceration
Hepatotoxicity	Toxic epidermal necrolysis
Reproductive	Urticaria
Amenorrhea	*Carcinogenesis*
Azospermia	Leukemia
Ovarian failure	Lymphoma
Neurologic	Squamous cell carcinoma
Mood alterations	
Seizures	

Side effects

The most common side effect is bone marrow toxicity. It is usually mild and transient after discontinuing the drug but may be severe and progressive. Nausea and vomiting are frequent side effects. Hepatotoxicity may be seen. Owing to mutagenic properties of all alkylating agents, patients receiving chlorambucil have an increased risk of developing a second malignancy, particularly leukemia and squamous cell carcinoma.[17, 18] Malignancy incidence increases with the duration of therapy and cumulative dosage.[19] Alopecia, anaphylaxis, urticaria and cutaneous drug eruptions have been reported. One of the miscellaneous but important rare side effects of chlorambucil is interstitial pneumonitis and pulmonary fibrosis. Ovarian atrophy and aspermia can be seen.

REFERENCES

1. Dantzig PI. Immunosuppressive and cytotoxic drugs in dermatology. Archives of dermatology 1974;110:393-406.
2. Shah N, Green AR, Elgart GW, Kerdel F. The use of chlorambucil with prednisone in the treatment of pemphigus. Journal of the American Academy of Dermatology 2000;42:85-8.
3. Begleiter A, Mowat M, Israels LG, Johnston JB. Chlorambucil in chronic lymphocytic leukemia: mechanism of action. Leukemia & lymphoma 1996;23:187-201.
4. Wilcox RA. Cutaneous T-cell lymphoma: 2014 update on diagnosis, risk-stratification, and management. American journal of hematology 2014;89:837-51.
5. Suarez AL, Querfeld C, Horwitz S, Pulitzer M, Moskowitz A, Myskowski PL. Primary cutaneous B-cell lymphomas: part II. Therapy and future directions. Journal of the American Academy of Dermatology 2013;69:343 e1-11; quiz 55-6.
6. Ryan E, Warren LJ, Szabo F. Necrobiotic xanthogranuloma: response to chlorambucil. The Australasian journal of dermatology 2012;53:e23-5.
7. Resnik BI, Rendon M, Kerdel FA. Successful treatment of aggressive pyoderma gangrenosum with pulse steroids and chlorambucil. Journal of the American Academy of Dermatology 1992;27:635-6.
8. Callen JP, Case JD, Sager D. Chlorambucil--an effective corticosteroid-sparing therapy for pyoderma gangrenosum. Journal of the American Academy of Dermatology 1989;21:515-9.
9. Chave TA, Mortimer NJ, Shah DS, Hutchinson PE. Chlorambucil as a steroid-sparing agent in bullous pemphigoid. The British journal of dermatology 2004;151:1107-8.
10. Milligan A, Hutchinson PE. The use of chlorambucil in the treatment of bullous pemphigoid. Journal of the American Academy of Dermatology 1990;22:796-801.
11. Mudun BA, Ergen A, Ipcioglu SU, Burumcek EY, Durlu Y, Arslan MO. Short-term chlorambucil for refractory uveitis in Behcet's disease. Ocular immunology and inflammation 2001;9:219-29.
12. Kaklamani VG, Kaklamanis PG. Treatment of Behcet's disease an update. Seminars in arthritis and rheumatism 2001;30:299-312.

13. O'Duffy JD, Robertson DM, Goldstein NP. Chlorambucil in the treatment of uveitis and meningoencephalitis of Behcet's disease. The American journal of medicine 1984;76:75-84.

14. Yazici H, Yurdakul S, Hamuryudan V. The management of Behcet's syndrome: how are we doing? Clinical and experimental rheumatology 1999;17:145-7.

15. Israel HL, McComb BL. Chlorambucil treatment of sarcoidosis. Sarcoidosis 1991;8:35-41.

16. Kataria YP. Chlorambucil in sarcoidosis. Chest 1980;78:36-43.

17. Burruss JB, Farmer ER, Callen JP. Chlorambucil is an effective corticosteroid-sparing agent for recalcitrant pyoderma gangrenosum. Journal of the American Academy of Dermatology 1996;35:720-4.

18. Effects of chlorambucil and therapeutic decision in initial forms of chronic lymphocytic leukemia (stage A): results of a randomized clinical trial on 612 patients. The French Cooperative Group on Chronic Lymphocytic Leukemia. Blood 1990;75:1414-21.

19. Palmer RG, Denman AM. Malignancies induced by chlorambucil. Cancer treatment reviews 1984;11:121-9.

20. Lorent A, Feermans W, Blondeel A, Meerts P, Achten G. [Sezary syndrome: treatment with a prednisolone-chlorambucil combination]. Dermatologica 1982;165:464-5.

21. Berglund G, Hansson L, Persson B, Vikgren P. Combined chlorambucil and prednisolone treatment of five patients with Wegener's granulomatosis. Acta medica Scandinavica 1972;191:5-9.

22. Westberg NG, Swolin B. Acute myeloid leukemia appearing in two patients after prolonged continuous chlorambucil treatment for Wegener's granulomatosis. Acta medica Scandinavica 1976;199:373-7.

23. Mamo JG. Treatment of Behcet disease with chlorambucil. A follow-up report. Archives of ophthalmology 1976;94:580-3.

24. Temime P, Berard P, Privat Y, Oddoze L, Marchand JP. [Behcet syndrome treated with chlorambucil]. Bulletin de la Societe francaise de dermatologie et de syphiligraphie 1969;76:433-4.

25. Eichhorn A, Siepmann M, Kirch W. [Chlorambucil treatment of Behcet's syndrome. Retrospective evaluation of two cases]. Medizinische Klinik 2010;105:20-5.

26. Case JD, Smith SZ, Callen JP. The use of pulse methylprednisolone and chlorambucil in the treatment of Sweet's syndrome. Cutis 1989;44:125-9.

27. Sinoway PA, Callen JP. Chlorambucil. An effective corticosteroid-sparing agent for patients with recalcitrant dermatomyositis. Arthritis and rheumatism 1993;36:319-24.