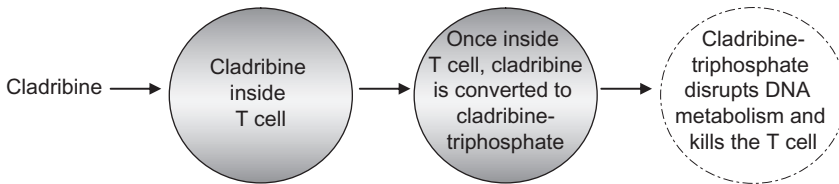


- Maintenance of the integrity of the blood–brain barrier (60). “Integrity of the blood–brain barrier” refers, in part, to the ability of the blood–brain barrier to serve as a wall against migrating immune cells.

e. Cladribine

Cladribine (2-chlorodeoxyadenosine) is a small molecule that is an analog of deoxyadenosine. When administered, cladribine is taken up by cells, including lymphocytes, and is phosphorylated to produce cladribine-triphosphate. Cladribine-triphosphate is then incorporated into the chromosome of lymphocytes during the normal activities of cell division and DNA repair. But when cladribine is incorporated into the cell’s DNA, the result is DNA stand breaks, and cell death by apoptosis (61,62), as indicated in the following diagram.



Cladribine’s selective action in killing lymphocytes results from the fact that lymphocytes have high levels of deoxycytidine kinase (63,64). This enzyme catalyzes the phosphorylation of cladribine, producing cladribine-triphosphate. Please note that conversion of cladribine to cladribine-triphosphate is required for incorporation of the drug into the chromosome. The killing action of cladribine is increased in cells that contain greater amounts of deoxycytidine kinase (65). Experimentally increased amounts of this enzyme in cells resulted in enhanced killing action by cladribine. One might expect cladribine to be broken down by adenosine deaminase, an enzyme present at strikingly high levels in lymphocytes (66). However, cladribine is distinguished in that it resists breakdown by this enzyme (67). Cladribine does not inhibit

⁶⁰Sheremata WA, Jy W, Delgado S, Minagar A, McLarty J, Ahn Y. Interferon- β 1a reduces plasma CD31 + endothelial microparticles (CD31+ EMP) in multiple sclerosis. *J. Neuroinflamm.* 2006;3:23–7.

⁶¹Szondy Z. The 2-chlorodeoxyadenosine-induced cell death signalling pathway in human thymocytes is different from that induced by 2-chloroadenosine. *Biochem. J.* 1995;311:585–8.

⁶²Van Den Neste E, Cardoen S, Husson B, et al. 2-Chloro-2'-deoxyadenosine inhibits DNA repair synthesis and potentiates UVC cytotoxicity in chronic lymphocytic leukemia B lymphocytes. *Leukemia* 2002;16:36–43.

⁶³Petzer AL, Bilgeri R, Zilian U, et al. Inhibitory effect of 2-chlorodeoxyadenosine on granulocytic, erythroid, and T-lymphocytic colony growth. *Blood* 1991;78:2583–7.

⁶⁴Sabini E, Hazra S, Konrad M, Lavie A. Elucidation of different binding modes of purine nucleosides to human deoxycytidine kinase. *J. Med. Chem.* 2008;51:4219–25.

⁶⁵Hapke DM, Stegmann AP, Mitchell BS. Retroviral transfer of deoxycytidine kinase into tumor cell lines enhances nucleoside toxicity. *Cancer Res.* 1996;56:2343–7.

⁶⁶Ungerer JP, Oosthuizen HM, Bissbort SH, Vermaak WJ. Serum adenosine deaminase: isoenzymes and diagnostic application. *Clin. Chem.* 1992;38:1322–6.

⁶⁷Piro LD, Carrera CJ, Beutler E, Carson DA. 2-Chlorodeoxyadenosine: an effective new agent for the treatment of chronic lymphocytic leukemia. *Blood* 1988;72:1069–73.