

active in cells with high levels of deoxycytidine kinase, such as lymphocytes (38,39). Cladribine is used to treat multiple sclerosis and a type of leukemia (hairy cell leukemia) (40).

The connection between deoxynucleotides and killing lymphocytes, as it applies to cladribine, is as follows. Inherited deficiencies of the enzyme adenosine deaminase interfere with lymphocyte development while sparing most other organ systems (41). The accumulation of deoxyadenosine nucleotides in the lymphocytes, that is, in lymphocytes of people suffering from adenosine deaminase deficiency, reduces the number of lymphocytes. As a consequence, the patients suffer from severe immunodeficiency.

Carson et al. (42) realized that the elimination of adenosine deaminase activity can halt lymphocytes that are pathological, such as the lymphocytes in leukemia (leukemia is a cancer of lymphocytes). This elimination was accomplished by cladribine. Cladribine, in effect, mimics the inherited disease (adenosine deaminase deficiency) because cladribine resists the effects of

adenosine deaminase. Cladribine naturally resists deamination catalyzed by adenosine deaminase. (For cladribine to be effective in destroying lymphocytes, it is not necessary that patients be suffering from adenosine deaminase deficiency.) Just as the normally occurring deoxyadenosine kills lymphocytes in people with the genetic disease adenosine deaminase deficiency, cladribine kills lymphocytes when administered to normal humans (43). It was about 10 years after the use of cladribine to treat leukemia that cladribine was first used to treat multiple sclerosis (44,45).

This summarizes the pathway of the discovery of cladribine for multiple sclerosis. First, it was known that an inherited genetic disease involved the accumulation of deoxyadenosine nucleotides in the cell, and resulted in death of lymphocytes. Second, researchers developed a drug that, when administered to a human subject, mimicked the effects of this disease (due to the inability of adenosine deaminase to act on the drug). Third, the drug was used to treat leukemia. Fourth, the drug was used to treat multiple sclerosis (46).

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