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Acyclic Nucleoside Phosphonate Analogues Markedly Enhance Natural Killer Activity in Mice
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Several members among the acyclic nucleoside phosphonate analogues are potent and selective inhibitors of various viruses, including herpesviruses and human immunodeficiency virus (HIV). Preliminary data from our group suggest that 9-(2-phosphonylmethoxyethyl)adenine (PMEA) enhances natural killer activity (NK) and stimulates interferon production in C57BL/6 mice. A single administration of a non-toxic dose of 25 mg PMEA/kg increases NK activity by 200% at days 2 and 3 post injection. The PMEA-induced NK enhancement is detectable up to day 6. The enhancement of NK activity induced by (*R,S*)-9-(3-fluoro-2-phosphonylmethoxypropyl)adenine (FPMPA) is substantial but less marked than observed for PMEA: NK activity increased starting from day 2 post injection and peaked at day 3. The greatest NK activity (70% increase with respect to controls) was achieved in mice treated with 50 mg/kg FPMPA (the maximum dose tested in our assay system). Since FPMPA is substantially less toxic than PMEA both in animals and in *in vitro* assays, our data do not exclude that a greater enhancement of NK activity could be obtained with higher doses of FPMPA. 3'-Azido-2',3-dideoxythymidine (AZT) is not effective in modulating NK activity at concentrations up to 30 mg/kg (slightly below its toxicity). Interferon (IFN) production clearly paralleled the enhancement of NK activity in mice exposed to PMEA or FPMPA, while AZT was ineffective in inducing IFN production. Our results suggest that acyclic nucleoside phosphonate analogues could, in addition to their prominent anti-herpes and/or anti-HIV activity, be of benefit in restoring some immune functions in immunocompromised hosts such as HIV- or herpesvirus-infected patients.

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Reversal of Established FeLV-FAIDS Infection After Adoptive Transfer of Activated Lymphocytes in Combination with AZT and Alpha Interferon NS Zeidner[1], CK Mathiason-DuBard[1], EA Hoover[1], [1]Department of Pathology, Colorado State University, Fort Collins, CO. 80523 U.S.A.

The treatment of presymptomatic FeLV-FAIDS viremia utilizing IFNα, alone or in combination with AZT, resulted in a significant reduction in circulating virus throughout a 49 day treatment period. However, the anti-FeLV effect of IFNα was limited by the production of antibodies to IFNα detected 7 weeks after the start of therapy. AZT alone had no effect on circulating virus load. To examine the hypothesis that combination treatment consisting of immune reconstitution plus IFNα and AZT would induce reversal of established retrovirus infection, asymptomatic cats were infused with activated lymphocytes, IFNα, and AZT 12 weeks after infection with FeLV-FAIDS. Recipient cats received weekly infusions of 1.45 $x10^8$ lymphocytes comprised of 98% T cells with an even distribution of CD4 and CD8 lymphocytes. Established FeLV-FAIDS infection was reversed in 4 of 6 cats by day 21 of the treatment period after 5 adoptive cell transfers. These cats remained negative for circulating virus during a 63 day treatment period (a total of 17 adoptive cell transfers) despite the elaboration of high titers of anti-IFNα antibodies. Sequential development of significant neutralizing antibody titers, specific for the virus envelope, were detected in those cats which reversed retroviremia, an antiviral response that failed to manifest itself in either placebo-treated control animals or in those cats that failed to respond to treatment. Three of six treated cats remained negative for FeLV antigen 95 days after treatment was discontinued. Treatment of cats with activated lymphocytes without concomitant chemotherapy failed to influence the course of established FeLV-FAIDS infection. These results suggest that combination therapy utilizing IFNα and adoptive lymphocyte transfer served to reconstitute humoral immunity, counteract retrovirus-induced immunosuppression and induce reversal of persistent, asymptomatic retroviremia. Supported by contract NO1-AI-72663, DTB, DAIDS, NIAID, NIH.