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Liposomal Encapsulation of Azidothymidine Results in Decreased Hematopoietic Toxicity and Enhanced Activity Against Murine Acquired Immunodeficiency Syndrome

By Nigel C. Phillips and Chris Tsoukas

This study has determined the effect of liposomal encapsulation on the hematopoietic toxicity and antiviral activity of 3′-azido-3′-deoxythymidine (AZT) in mice. Daily intravenous administration in the dose range 0.4 to 10 mg/kg body weight for 5 days significantly depressed bone marrow cellularity with a corresponding decrease in red blood cell, blood neutrophil, and monocyte numbers. Maximum toxicity was seen at 2 mg/kg or greater. Liposomal encapsulation of AZT and administration at 2 mg/kg abrogated the toxicity of AZT. The neutrophil inflammatory response to thioglycollate injected intraperitoneally was significantly inhibited by AZT at all doses, whereas liposomal AZT was without effect. The inhibitory activity of AZT against Concanavalin A (Con A)-stimulated splenic lymphocyte proliferation in vitro was reduced on liposomal encapsulation of AZT, while treatment of mice with liposomal AZT but not free AZT resulted in a significant reduction of Con A-stimulated proliferation. Liposomal AZT was more effective than AZT in preventing the development of plasma reverse transcriptase activity and the depletion of Thy 1.2⁺-L3T4⁺ T cells after infection of mice with LP-BM5 retrovirus. These results indicate that AZT-induced hematopoietic toxicity may not be a limiting factor for antiviral therapy, and that the use of liposomes to deliver AZT results in enhanced antiretroviral activity in mice.
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AZIDOTHYMIDINE (AZT) was initially reported as being capable of inhibiting human immunodeficiency virus (HIV) replication and its subsequent cytopathic effects[1]: further studies demonstrated that AZT was phosphorylated to the 5′-triphosphate and preferentially interacted with virus reverse transcriptase.[2] AZT significantly inhibits mitogen-stimulated proliferation of normal human lymphoid cells at antiviral concentrations,[1,2] as well as inhibiting mitogen-stimulated growth and DNA repair in human peripheral lymphocytes at therapeutic levels.[3] Short-term dose regimens of AZT (6 weeks) were effective in restoring white blood cell (WBC) counts and eliminating HIV from the circulation in patients with acquired immunodeficiency syndrome (AIDS).[4] Longer study periods (≥ 24 weeks) showed that while AZT treatment decreased mortality and the frequency of opportunistic infections, significant bone marrow depression occurred.[5-9] Such side effects are dose-related.[10] Similar bone marrow toxicity, necessitating dose reduction or cessation, has been observed in children with asymptomatic HIV infection receiving continuous intravenous (IV) infusion of AZT.[8] Long-term bone marrow failure (>6 months) associated with AZT therapy has been reported,[11] as well as agranulocytosis after short-term (1 week) therapy with AZT.[12] The termination of AZT treatment has been shown to be associated with increased levels of viral core protein p24 and decreased $CD4^+$ cells,[13] and may lead to increased viral replication.[14]

There is little information derived from animal models on the toxicity of AZT. AZT suppresses mouse viremia and retroviral disease in mice,[15-18] but significant short- and long-term hematologic changes resulting from bone marrow toxicity are observed at therapeutic doses.[15,19]

Liposomes, small phospholipid vesicles within which drugs can be entrapped,[20] have been shown to reduce the systemic toxicity of a number of chemotherapeutic agents in preclinical and clinical trials.[21-25] The reduction in bone marrow toxicity seen after liposomal encapsulation of a muramyl peptide, MTP-PE,[26] and of doxorubicin[21] in animal models, in conjunction with the tissue distribution profile of 99mTc-labeled liposomes in humans,[27] indicates that liposomal administration results in reduced bone marrow toxicity of chemotherapeutic agents. The localization of liposomes in organs rich in tissue-fixed macrophages–the liver, spleen, lungs, and kidney–in conjunction with their poor localization within the bone marrow may provide a mechanism for reducing the toxicity of agents such as AZT.

In this study we have investigated the potential of liposomal encapsulation of AZT for reducing hematopoietic toxicity and for enhancing antiviral activity in a murine model of AIDS.[28] Our results indicate that liposomal encapsulation of AZT results not only in a significant reduction in the toxicity of AZT toward bone marrow erythroid and myeloid precursors, but also in a significant enhancement of antiretroviral activity.

MATERIALS AND METHODS

AZT. AZT was obtained from the Sigma Chemical Company Ltd (St Louis, MO), and stored at −30°C. Solutions of AZT were prepared in apyrogenic 0.85% NaCl, sterile filtered (0.2 μ), and used immediately. Endotoxin was not detected (MA Bioproducts, Walkersville, MD; QCL 1000 endotoxin assay kit).

Liposomes. Liposomes were prepared from dipalmitoylphosphatidylcholine (DPPC) or distearoylphosphatidylcholine (DSPC) and dimyristoylphosphatidylglycerol (DMPG) (molar ratio 10:1; all phospholipids from Avanti Polar Lipids, Pelham, AL). Phospholipids were dissolved in anhydrous chloroform, placed in sterile, pyrogen-free round bottomed glass flasks, and subjected to rotary evaporation at 65°C. Apyrogenic 0.85% NaCl or AZT (2.5 to 10 mg/mL in 0.85% NaCl) was added to the dried phospholipids, which were then allowed to hydrate at 20°C for 30 minutes. The

From The Montreal General Hospital Research Institute and the Department of Medicine, McGill University, Montreal, Quebec, Canada.

Submitted February 25, 1991; accepted October 18, 1991.

Supported by a Grant-in-Aid from the Medical Research Council of Canada.

Address reprint requests to N.C. Phillips, PhD, the Montreal General Hospital Research Institute, 1650 Cedar Ave, Montreal, Quebec, Canada H3G 1A4.

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flask and contents were agitated at 65°C until liposomes had been formed (1 to 2 minutes). Unincorporated AZT was removed by centrifugation washing (25,000g for 10 minutes at 4°C, three washes), the final liposome pellet being resuspended in 0.85% NaCl (5 μmol/mL). Sterility and endotoxin determinations were negative. Liposomal AZT was measured by placing a sample of liposomal AZT (10 to 25 μL) in 2.0 mL methanol for 30 seconds, followed by the addition of 1.0 ml H_2O. The absorbance was determined at 265 nm using control liposomes as blank. Standard curves of AZT in the absence and presence of liposomes were used to determine the amount of liposome-incorporated AZT.

Liposomal retention of AZT. Liposomes containing AZT (10 μmol phospholipid hydrated with 10 mg/mL AZT at a final concentration of 5 μmol phospholipid/mL) were incubated in 0.85% NaCl at 4°C or 37°C. Samples (100 to 250 μL) were removed at intervals, diluted to 1.5 mL with 0.85% NaCl, and centrifuged at 13,000g for 10 minutes at 4°C. The supernatant was discarded, and the pellet resuspended in 100 to 250 μL 0.85% NaCl. AZT determination was performed as described above.

Administration of free and liposomal AZT to mice. Male CD_1 or C57BL/6 mice (Charles River, St Constance, Quebec, Canada: 7 to 9 weeks old, specific pathogen-free) received AZT (0.4, 2, or 10 mg/kg), control liposomes (2.5 μmol), or liposomal AZT (0.4 to 10 mg/kg) via a lateral tail vein in a dose volume of 0.2 mL. Treatment was performed for 5 days, and toxicity determined as described below on day 6.

Red blood cell (RBC) and leukocyte determination. A sample of heparinized blood (250 μL) was obtained from the retro-orbital plexus. RBCs (1/500 dilution in 0.85% NaCl) and leukocytes (1/10 in Turk's solution) were determined with an hematocytometer. Differential counts were determined after staining thin-film smears with hematoxylin/eosin.

Bone marrow cellularity. A femur was removed, and all extraneous tissue removed. The condyles were cut, and the bone marrow flushed with 3.0 mL MEM using a no. 26 gauge needle. Total cell counts were determined as described above.

Bone marrow localization of free and liposomal AZT. AZT (2 mg/kg body weight) containing [^{3}H-methyl] AZT (5 μCi/mouse; Sigma, specific activity 1 mCi/mmol) or liposomal AZT/[^{3}H-methyl] AZT (2 mg/kg body weight AZT/5 μCi [^{3}H-methyl] AZT mouse) was injected IV into groups of three CD_1 mice. Bone marrow cells were collected 1 to 5 hours later as described above, and the radioactivity determined by scintillation counting in a β-counter with automatic quench and chemiluminescence correction.

Neutrophil inflammatory response. Groups of five male C57BL/6 mice were treated with free or liposomal AZT in the dose range 0.4 to 10 mg/kg for 5 days. On the sixth day each mouse was injected intraperitoneally (IP) with 1.0 mL Brewer's thioglycollate broth. The mice were killed 5 hours later, and the peritoneal cavity injected with 10.0 mL 0.85% NaCl. After gentle massage the peritoneal contents were removed, the volume noted, and the number of neutrophils determined using a hematocytometer.

Spleen lymphocyte responses to Concanavalin A (Con A). Normal CD_1 mice (in vitro treatment) or CD_1 mice that had received free or liposomal AZT for 5 consecutive days (in situ treatment) were killed, and their spleens removed under aseptic conditions. The spleens were disrupted by the injection of MEM containing Earle's salts, glutamine, nonessential amino acids, and sodium pyruvate (all from Flow Laboratories, Mississauga, Ontario, Canada) and gentamycin (Garamycin; Schering Canada, Pointe-Claire, Canada; 50 μg/mL). After washing by centrifugation at 150g for 10 minutes at 4°C, the cells were resuspended in MEM, layered on Lymphoprep M (Cederlane Laboratories, Hornby, Ontario, Canada), and centrifuged at 500g for 20 minutes at 20°C. The pellet, containing RBCs, neutrophils and monocytes, was discarded. The interface cell layer, composed of greater than 95% lymphocytes, was removed, washed with MEM by centrifugation at 150g for 10 minutes at 4°C, and resuspended in MEM/2.5% heat-treated bovine calf serum (Flow Laboratories). Samples (200 μL) containing 2×10^5 viable cells were placed in the wells of tissue culture microtiter plates. For the in vitro treatment, control liposomes (100 nmol DSPC/DMPG), liposomes containing AZT, or AZT were added to triplicate wells. Con A (Sigma) in 20 μL MEM was immediately added to appropriate wells of both the in vitro and in situ AZT treatments to give a final mitogen concentration of 4.0 μg/mL. The plates were incubated at 37°C for 48 hours in a humid atmosphere of 5% CO_2, and cell proliferation determined by counting 100-μL samples from each well in a hematocytometer (in vitro treatment), or by adding 0.5 μCi [^{3}H]-methylthymidine (specific activity 1 mCi/mmol; ICN Radiochemicals, Irvine, CA) in 20 μL MEM to each well and harvesting the cells with a cell harvester after a further 18 hours of incubation (in situ treatment). Incorporated radioactivity was determined in a β-counter with quench and chemiluminescence correction.

Murine AIDS. Female C57BL/6 mice (6 to 8 weeks old; Charles River, St Constance, Quebec, Canada) were infected with LP-BM5 retrovirus by IP injection. Treatment with AZT (2 mg/kg IV) or liposomal AZT (2.5 μmol phospholipid containing 2 mg/kg AZT IV) was started 7 days after retroviral infection. Treatment was continued three times weekly for up to 6 weeks.

T-cell enumeration. Single cell suspensions of spleen lymphocytes were obtained by gentle mechanical disruption with NH_4Cl lysis of RBCs. Total T cells and $CD4^+$ cells were determined by incubation with fluorescein isothyocyanate-labeled anti-Thy1.2 and phycoerythrin-labeled anti-L3T4 (GK1.5) monoclonal antibodies (both from Becton Dickinson, Mountain View, CA) and analysis on a FACS 440. $CD4^+$ cells were determined as a percentage of the total T-cell population.

Reverse transcriptase (RT). Plasma RT activity was assayed using a modification of the procedure of Ohnota et al.[17] Plasma (200 μL) was centrifuged at 13,000g for 30 minutes at 4°C. The supernatant (180 μL) was removed, and the pellet resuspended in 25 μL 0.1 mol/L TRIS-HCl, pH 7.4, containing 5 mmol/L DTT, 10 mmol/L $MgCl_2$, 10 mmol/L KCl, and 0.5% Nonidet p40 (Sigma). Triplicate samples (10 μL) were incubated with 50 μL 0.1 mol/L TRIS-HCl, pH 7.4, containing 1 μCi [^{3}H]-TTP (Amersham International, Amersham, England; specific activity 1 mCi/mmol), 5 mmol/L DTT, 1 μmol poly (A)-poly (T_{15}) (Sigma), and 0.5% Nonidet p40 in 96-well microtiter plates. Incubation was performed at 37°C for 60 minutes, and the reaction terminated by the addition of 100 μL 12.5% TCA. Incubation mixtures were collected into glass-fiber filters, washed with distilled H_2O, and dried. Radioactivity was determined by liquid scintillation β-counting with quench and chemiluminescence correction. Purified avian myeloblastoma RT (Sigma) was used as a positive control.

Statistical analysis. Statistical analysis (Student's *t*-test, Wilcoxon rank sum with Mann-Whitney U-test or ANOVA) was performed out using GB-STAT Professional (Dynamic Microsystems, Inc, Silver Spring, MD).

Animal experimentation. All animal experimentation procedures were performed according to guidelines established by the Canadian Council for Animal Care.

RESULTS

Liposomal incorporation and retention of AZT. Liposomal incorporation of AZT corresponded to inclusion within the aqueous phase of the liposome. Using AZT at 10 mg/mL to hydrate dried films of DPPC/DMPG and DSPC/

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DMPG, liposomal incorporation was 250 ± 12 and 240 ± 15 μg/10 μmol phospholipid, respectively (mean ± SD from four experiments). Incubation of these liposomes at 4°C did not result in the loss of AZT from the liposomes (Fig 1). Incubation of DPPC/DMPG liposomes at 37°C resulted in a 96% loss of AZT over a period of 24 hours; in contrast, DSPC/DMPG liposomes incubated at 37°C lost 64% of incorporated AZT (Fig 1). All subsequent experiments were performed using liposomes formulated from DSPC/DMPG.

Bone marrow localization of free and liposomal AZT. AZT (as [^{3}H]-methyl AZT) levels in the bone marrow remained constant 1 hour after injection and were associated with the cellular fraction (0.018% ± 0.004%/10^7 cells). Liposomal AZT was not detectable (<0.00001%/10^7 cells).

Hematologic toxicity of free and liposomal AZT. Treatment of mice with free AZT in the dose range 0.4 to 10 mg/kg for 5 days resulted in a dose-dependent reduction of bone marrow cellularity, RBCs, and leukocytes (Fig 2). Significant reductions in RBCs and leukocytes were seen at doses of 10 and 2 mg/kg ($P < .01$ and $P < .05$, respectively, Student's two-tailed t-test), but not at 0.4 mg/kg. The reduction in bone marrow cellularity was significant at all AZT doses ($P < .01$ to $P < .05$). Control liposomes or liposomal AZT in the dose range 0.4 to 10 mg/kg had no effect on bone marrow cellularity, RBCs, or leukocytes (Fig 2).

Peripheral blood leukocyte differentials. Free AZT at doses of 0.4 to 10 mg/kg induced a significant ($P < .05$, two-way ANOVA), dose-related reduction in the proportion of mature neutrophils (40% to 25% of control), with a corresponding increase in the proportion of immature neutrophils (160% to 260% of control). There was a total ablation of monocytes at the highest dose of free AZT, and significant ($P < .05$) reductions at the two lower doses (40% and 28% of control, respectively). There was no significant change in the proportion of lymphocytes at any dose of free AZT. The administration of control liposomes

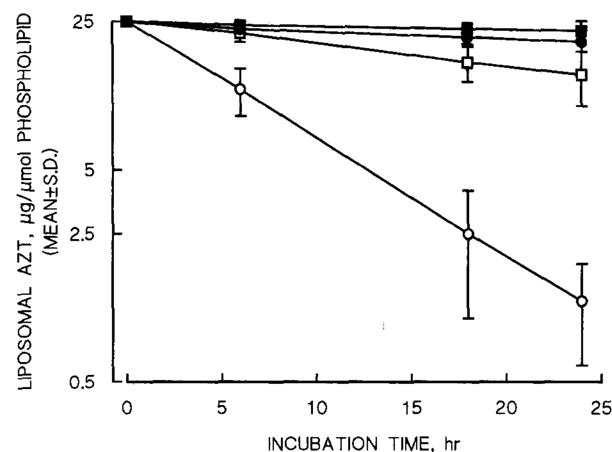

Fig 1. Liposomal retention of AZT. DSPC/DMPG or DPPC/DMPG liposomes containing AZT were incubated at 4°C or 37°C. Liposomal AZT was determined at the indicated times. (■—■), DSPC/DMPG 4°C; (□—□), DSPC/DMPG 37°C; (●—●), DPPC/DMPG 4°C; (○—○), DPPC/DMPG 37°C. Representative experiment of four.

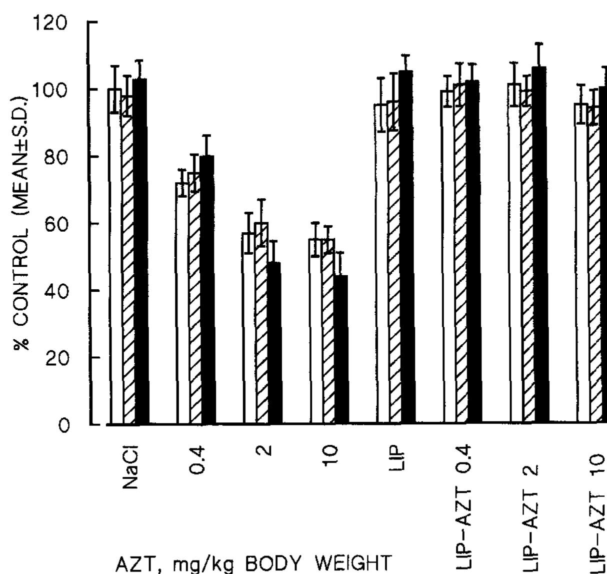

Fig 2. Hematopoietic toxicity of AZT and liposomal AZT. Groups of five mice were treated with AZT, liposomes (LIP), or liposomal AZT (LIP-AZT) for 5 days. Bone marrow cellularity, erythrocyte and leukocyte numbers were determined on day 6. AZT treatment at 0.4 to 10 mg/kg resulted in a significant decrease in bone marrow cellularity ($P < .05$ to $P < .01$, Student's t-test) and a significant decrease in erythrocyte and leukocyte numbers at 2 and 10 mg/kg ($P < .05$ and $P < .01$, respectively). The difference between AZT and liposomal AZT for all cell populations was highly significant ($P < .01$, three-way ANOVA). (□), Bone marrow cells; (▨), leukocytes; (■), erythrocytes. Mean ± SD of three experiments.

or liposomal AZT did not change the leukocyte differential from that seen in control, untreated mice.

Inflammatory neutrophil response. The administration of free AZT (0.4 to 10 mg/kg body weight) resulted in a significant and dose-related inhibition (43% to 69%, respectively) of the neutrophil inflammatory response against thioglycollate (Student's t-test for individual doses, $P < .01$; ANOVA between groups, $P < .001$). Control liposomes or liposomal AZT up to 10 mg/kg had no significant effect on the neutrophil inflammatory response, although a trend toward a reduced response at 10 mg/kg body weight (11% inhibition) was observed.

Lymphocyte mitogenic response. The administration of AZT (0.4 to 10 mg/kg body weight) or empty liposomes for 5 days had no significant effect on the subsequent in vitro responsiveness of spleen lymphocytes toward Con A (Fig 3). In contrast, the administration of liposomal AZT at 2 mg/kg body weight resulted in a significant reduction of 40% ($P < .01$, Wilcoxon-Mann-Whitney rank test) in the stimulation index (Fig 3). Treatment of splenic lymphocytes in vitro with AZT in the dose range 0.05 to 10 μg/mL resulted in a significant ($P < .05$, ANOVA) and dose-related reduction in their ability to respond to Con A (Fig 4). Liposomal encapsulation of AZT (0.25 to 2.5 μg/mL) resulted in a 10-fold decrease in potency compared with AZT (Fig 4).

Thy 1.2$^+$/L3T4$^+$ T cells. There was a transient increase in the proportion of Thy 1.2$^+$/L3T4$^+$ T cells 7 days after LP-BM5 infection (Fig 5). Thy 1.2$^+$/L3T4$^+$ T cells were

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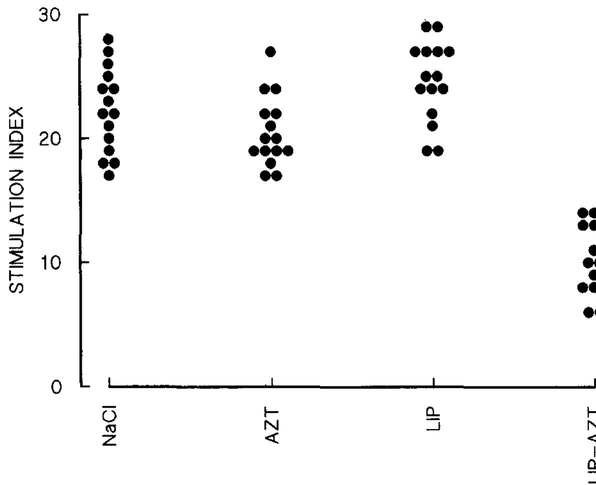

Fig 3. Spleen lymphocyte mitogenic response to Con A after free or liposomal AZT treatment in situ. Groups of five mice were treated with free AZT, liposomes (LIP), or liposomal AZT (LIP-AZT) for 5 days. Free AZT or liposome treatment had no effect on the stimulation index. The decrease in stimulation indices after liposomal AZT treatment was significant ($P < .001$, Wilcoxon rank sum with Mann-Whitney U-test). Individual results from three experiments.

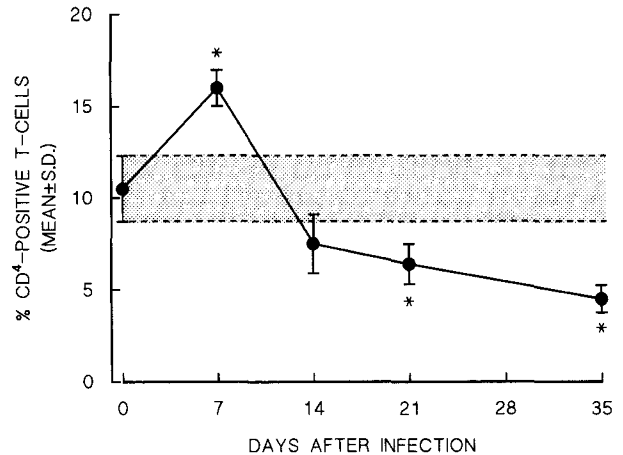

Fig 5. Spleen Thy $1.2^+/CD4^+$ T cells in LP-BM5–infected mice. Groups of five female C57BL/6 mice were infected with LP-BM5 leukemia virus. Splenic Thy $1.2^+/CD4^+$ T cells were determined at the indicated timepoints after infection. The elevation at day 7 and the depressed levels at days 21 and 35 were significantly different from control values ($P < .01$, Student's *t*-test for unpaired data). Representative result from three experiments.

significantly reduced compared with control mice at 21 and 35 days postinfection ($P < .001$, Student's *t*-test for unpaired data). Treatment with AZT at 2 mg/kg body weight did not prevent the LP-BM5–induced reduction in Thy1.2^+/$L3T4^+$ T cells (Fig 6), whereas liposomal AZT treatment at 2 mg/kg body weight resulted in normal Thy1.2^+/$L3T4^+$ positive T-cell levels (Fig 6).

Plasma RT activity. Plasma RT activity increased 35-fold over background activity during the experimental period of 35 days (Fig 7). AZT treatment at 2 mg/kg retarded but did not inhibit RT activity (Fig 7). Liposomal

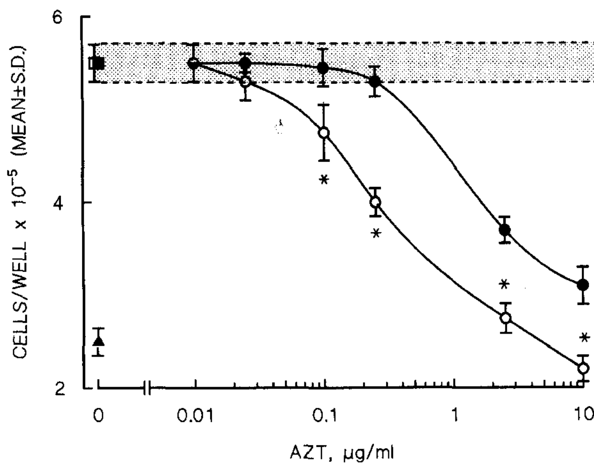

Fig 4. Spleen mitogenic response to Con A after free or liposomal AZT treatment in vitro. Spleen lymphocytes from groups of five mice were pooled, and 2.5×10^5 cells in 200 µL medium (▲) plated in triplicate in 96-well tissue culture plates. Incubation with Con A resulted in an increase in viable cell numbers to 5.4×10^5/well (□). AZT (○—○) in the dose range 0.025 to 10 µg/mL inhibited cell proliferation. Liposomal AZT (●—●) also inhibited cell proliferation but with a relative potency of 0.12 compared with free AZT (calculated using the least squares method). Liposomes alone (■) had no effect on mitogenesis. *, Significantly different from liposomal AZT-treated splenocytes ($P < .01$, Student's *t*-test for unpaired data). Representative result from three experiments.

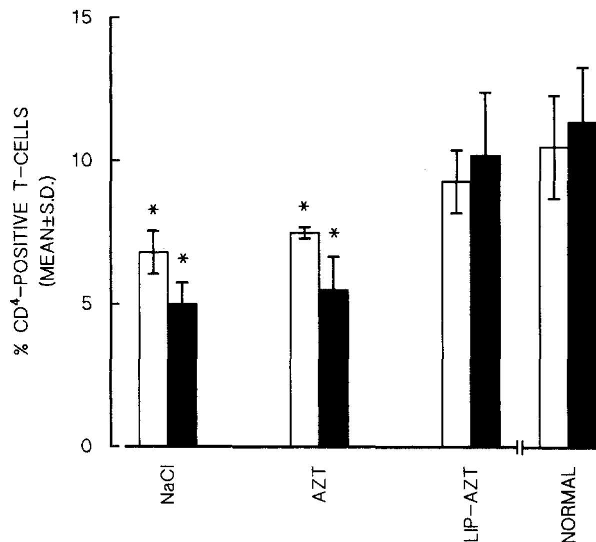

Fig 6. Effect of AZT treatment on LP-BM5 leukemia virus-induced suppression of splenic Thy $1.2^+/CD4^+$ T cells. Groups of five C57BL/6 mice infected with LP-BM5 leukemia virus were treated three times weekly with AZT (2 mg/kg) or liposomal AZT (2.5 µmol phospholipid/2 mg/kg AZT) starting 7 days after infection. Splenic Thy $1.2^+/CD4^+$ T cells were determined at 3 (□) and 5 weeks (■) after infection. *, Significantly different from normal, uninfected mice ($P < .01$, Student's *t*-test for unpaired data). Representative result from three experiments.

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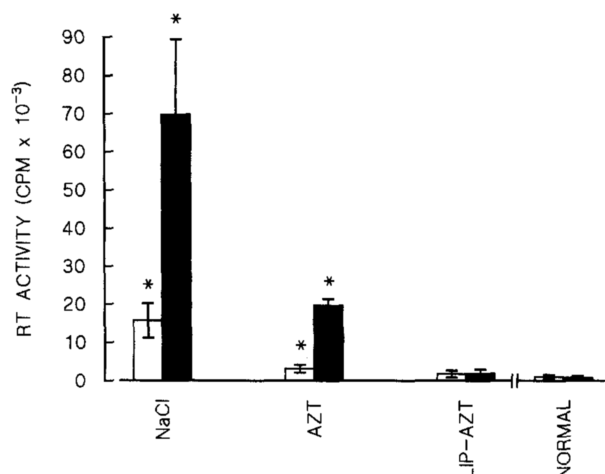

Fig 7. Effect of AZT treatment on plasma RT activity. Groups of five C57BL/6 mice infected with LP-BM5 leukemia virus were treated three times weekly with AZT (2 mg/kg) or liposomal AZT (2.5 μmol phospholipid/2 mg/kg AZT) starting 7 days after infection. Plasma RT activity was measured at 3 (□) and 5 weeks (■) after infection. *, Significantly different from normal, uninfected mice ($P < .01$, Student's *t*-test for unpaired data). Representative result from three experiments.

AZT at 2 mg/kg suppressed the development of RT activity to within background levels (Fig 7).

DISCUSSION

AZT was well retained in liposomes formulated from either DPPC/DMPG or DSPC/DMPG and stored at 4°C. Incubation of the liposomes at 37°C showed that DSPC/DMPG liposomes retained AZT better than DPPC/DMPG liposomes (t½ of 13 *v* 4 hours, respectively). These times are in agreement with previously published studies on the liposomal retention of water-soluble molecules.[29,30]

This study clearly demonstrates that AZT has profound acute toxicity against myelopoiesis and erythropoiesis in mice when administered systemically. The short-term dosing regimen used in this study reduced the number of RBCs and circulating monocytes and neutrophils, presumably as a result of toxicity toward their precursor cells in the bone marrow. The encapsulation of AZT within liposomal carriers abrogated the hematopoietic toxicity of AZT, resulting in normal RBC and circulating neutrophil and monocyte levels. These observations are consistent with the low targeting efficiency of liposomal AZT to the bone marrow. Therefore, the encapsulation of AZT within liposomal carriers is an effective way in which to reduce its toxicity against bone marrow cells.

A number of studies have demonstrated that AZT has significant in vitro toxicity toward bone marrow-derived rodent and human granulocyte/monocyte and early and late erythroid progenitor cells.[31-33] Our results confirm that AZT exerts its acute in vivo toxic effect on bone marrow at the level of RBC and neutrophil/monocyte production, and is capable of significantly inhibiting the neutrophil inflammatory response. Liposomal encapsulation of AZT eliminated the hematopoietic toxicity and restored a normal neutrophil inflammatory response, providing confirmation that the observed reduction in hematopoietic toxicity is expressed at a functional level.

In contrast to its toxicity against neutrophil and monocyte precursors in the bone marrow, free AZT appeared to have little effect on mature lymphocytes in the spleen. Mitogenic responsiveness in vitro toward Con A remained unchanged after treatment in situ with AZT for 5 days. Liposomal AZT treatment resulted in a significant reduction in the ability of spleen lymphocytes to respond to Con A. The almost exclusive localization of liposomes within splenic macrophages[34] indicates that liposomal therapy results in the formation of a depot of AZT followed by its release within the spleen. Liposomal encapsulation of AZT resulted in a 10-fold decrease in direct toxicity against purified spleen lymphocytes in vitro, again indicating that phagocytic cells are required for the expression of AZT activity after liposomal encapsulation.

Infection of C57BL/6 mice with LP-BM5 leukemia retrovirus results in a disease (murine AIDS or MAIDS) similar to HIV-induced AIDS.[28,35-39] AZT treatment prolongs the survival of LP-BM5–infected mice,[18] inhibits retrovirus-induced immunosuppression,[17,18] and retards alterations in lymphoid cell populations[40] and erythroid progenitors.[19] Viremia[18] and plasma RT activity[17] are also reduced but not eradicated by AZT treatment. The results of this study show that AZT treatment only delayed the development of plasma RT activity by 14 days, and had no effect on retrovirus-induced depression of Thy 1.2^+/$L3T4^+$ T cells. In contrast, liposomal AZT prevented retrovirus-induced elevation of plasma RT activity, and maintained normal numbers of Thy 1.2^+/$L3T4^+$ T cells. RT activity is an accepted means of determining retrovirus levels[41]: the ability of liposomal AZT therapy to maintain T-helper subset levels and to inhibit viremia strongly indicate a fundamental difference in activity between AZT and liposomal AZT.

HIV infection in humans is associated with phagocytic cell dysfunction,[42,43] and the macrophage has been identified as a primary site of infection in MAIDS.[44] Targeting AZT or other nucleoside analogues to tissue macrophages or monocytes via the use of liposomes[45] or immunoliposomes[46] may have additional impacts on retrovirus-induced immune suppression and viral dissemination via infection of these migratory cells.[47] We are currently investigating the impact of liposomal AZT on monocyte/macrophage defense functions in MAIDS.

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