To the editor:

The management of meningeal lymphoma in patients with HIV in the era of HAART: intrathecal depot cytarabine is effective and safe

Meningeal involvement in patients with AIDS-related non-Hodgkin lymphoma (ARL) is common; it confers a dismal prognosis, and therapy usually involves frequent lumbar punctures. In 137 individuals with ARL in the era of highly active antiretroviral therapy (HAART), 22 had meningeal involvement at presentation. We compared the use of standard alternating intrathecal methotrexate and cytarabine with a sustained-release formulation of intrathecal cytarabine (DepoCyt) that maintains concentrations in the cerebrospinal fluid (CSF). There were no significant changes in overall survival, the rate of fall of CSF protein, and remission rates defined as absence of lymphomatous cells in the CSF and a CSF protein level less than 0.4 mg/L. DepoCyt appears safe and effective in patients with ARL and meningeal disease and reduces the number of intrathecal administrations required.

Despite the progress that has been made in controlling cancer at most sites in the body, the outcome of individuals affected by meningeal infiltration by cancer remains poor. As few patients with this condition survive for more than several months, the management of individuals with meningeal disease remains a great challenge.1-3 The direct intrathecal instillation of anticancer drugs is one approach that has successfully been used by oncologists, particularly in the treatment and prevention of leptomeningeal leukemias and lymphomas, to circumvent the pharmacologic sanctuary resulting from the blood-brain barrier. Only methotrexate and cytarabine (cytosome arabinoside [Ara-C]) are routinely administered intrathecally, and both are specific to the cell cycle’s S phase. Therefore, both agents would appear most effective when cytotoxic concentrations are maintained. Achieving this has necessitated prolonged and frequent course of lumbar punctures, which are both painful and labor intensive.

An encapsulated microvesicular liposome preparation named DepoCyt (Sykepharma, London, United Kingdom) drastically changes the pharmacokinetics of the free cytarabine released15 such that the mean elimination t½ of the depot formulation of free cytarabine is 130 to 277 hours, versus 3.4 hours for native cytarabine.6-8 In 2 randomized clinical trials by Glantz et al that have recruited a total of 89 patients,9,10 DepoCyt produced a high response rate, comparable with either methotrexate or free cytarabine, and delayed neurologic progression. The DepoCyt regimen also produced a higher clearance rate of lymphoma from the CSF and prolonged time to neurologic progression compared with conventional intrathecal chemotherapy in a randomized controlled trial.11 DepoCyt has not been evaluated in HIV-1–seropositive individuals. Because patients with ARL have frequent meningeal involvement (a situation complicated by frequent poor compliance in this vulnerable patient group12,13), we compared the efficacy of DepoCyt with that of alternating intrathecal methotrexate and cytarabine.

Since 1996, the start of the HAART era, 137 individuals at The Chelsea and Westminster Hospital have been diagnosed with biopsy-confirmed ARL, including 22 (16%) with meningeal involvement at presentation; these comprised 0.4% of all HIV-1–seropositive individuals with whom follow up was conducted during this time. Meningeal involvement was defined as abnormal enhancement on a brain computerized tomography or magnetic resonance scan and/or the presence of lymphoma cells in the CSF.

In addition to their systemic chemotherapy, they received intrathecal chemotherapy. Up until 2004, this comprised alternating intrathecal methotrexate (12.5 mg) and intrathecal cytarabine (50 mg), given twice a week for 4 weeks, then once a week for 4 weeks, then once a fortnight for 8 weeks, and then monthly until systemic chemotherapy was completed, approximately 18 intrathecal procedures in total.14 Since that time, DepoCyt, a slow-release formulation of cytarabine, has been used alone, comprising a 50-mg intrathecal injection alone every 2 weeks for 2 months followed by monthly injections for 6 months, for a total of 10 intrathecal installations. Each DepoCyt injection was accompanied by 4 mg dexamethasone given orally or intravenously twice a day for 5 days.

There were no significant differences in overall survival between individuals who received either intrathecal alternating

Figure 1. Survival and change in CSF protein with DepoCyt versus standard alternating methotrexate and cytarabine. (A) A Kaplan-Meier curve demonstrating the overall survival of individuals with ARL and meningeal disease, treated with either DepoCyt or alternating intrathecal installations of methotrexate and cytarabine. (B) A comparison of the rate of fall of CSF protein from the first intrathecal installation to 1 month. The median with the standard error of the mean is shown.
methotrexate and cytarabine, or intrathecal DepoCyt (Figure 1A; log-rank, \( P = .26 \)). Table 1 demonstrates the characteristics of 17 HIV-1–infected individuals with meningeal involvement at ARL presentation who received alternating intrathecal methotrexate and cytarabine compared with 5 patients who received DepoCyt since 2004. There were no differences that approached significance at baseline between the 2 groups, including no difference in the initial CD4 protein, mg/L (Mann-Whitney \( U \) test, \( P = .59 \)). The repeated intra-CSF administrations necessary to accomplish this obviously pose difficulties and Ommaya reservoirs have been implanted to permit repeated intra-CSF installations.22 This in turn requires anesthesia and surgery, though their use has not been reported in the setting of ARL.

Standard treatment for meningeal disease is time consuming, painful, labor intensive, and the subject of much adverse media and journal coverage when errors occur.23.24 As the prognosis of patients with meningeal disease has not changed for 3 decades,2 any therapy that reduces pain, time, and labor for both patients and treating physicians without a deleterious effect on outcome should be considered as standard therapy. As improved systemic therapy has ironically resulted in greater numbers of patients with leptomeningeal disease, DepoCyt should also be considered in a trial of CNS prophylaxis in patients with ARL and others at high risk of meningeal relapse.

### Table 1. The clinicopathologic features of 22 ARL patients with meningeal disease treated with different intrathecal regimens

<table>
<thead>
<tr>
<th>IPI group, no. (%)</th>
<th>Male, no. (%)</th>
<th>Mean age, y (range)</th>
<th>CD4 &lt; 100/mm(^3), no. (%)</th>
<th>Prior ADI, no. (%)</th>
<th>On HAART at NHL diagnosis, no. (%)</th>
<th>Viral load less than 50 copies/mL, no. (%)</th>
<th>Bone marrow involved by NHL, no. (%)</th>
<th>Burkitt histology, no. (%)</th>
<th>ECOG PS, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI</td>
<td>3 (14)</td>
<td>6 (27)</td>
<td>8 (36)</td>
<td>16 (86)</td>
<td>15 (68)</td>
<td>15 (68)</td>
<td>11 (50)</td>
<td>8 (36)</td>
<td>1 (86)</td>
</tr>
<tr>
<td>HI</td>
<td>2 (9)</td>
<td>2 (12)</td>
<td>2 (9)</td>
<td>6 (36)</td>
<td>6 (36)</td>
<td>12 (71)</td>
<td>9 (53)</td>
<td>7 (41)</td>
<td>1 (88)</td>
</tr>
<tr>
<td>H</td>
<td>13 (59)</td>
<td>6 (27)</td>
<td>4 (27)</td>
<td>4 (27)</td>
<td>17 (100)</td>
<td>3/21 (14)</td>
<td>3/16 (19)</td>
<td>3/21 (14)</td>
<td>1 (80)</td>
</tr>
</tbody>
</table>

Overall, DepoCyt is safe and effective in HIV-1–positive individuals with lymphomatous meningeal infiltration and has significant obvious advantages in its frequency of administration (18 vs 10 installations). It offers a significant alternative to the limited armamentarium of intrathecal agents in a group of individuals with well-documented issues with compliance18 and adherence.13,19

The leptomeninges and CSF pose a specific cytokinetic problem for oncologists because CSF concentrations of drugs need to be higher than any plasma-based administration can achieve (in either the plasma or CSF), and malignant cells within the CSF tend to proliferate slowly.2,20,21 The repeated intra-CSF administrations necessary to accomplish this obviously pose difficulties and Ommaya reservoirs have been implanted to permit repeated intra-CSF installations.22 This in turn requires anesthesia and surgery, though their use has not been reported in the setting of ARL.

Standard treatment for meningeal disease is time consuming, painful, labor intensive, and the subject of much adverse media and journal coverage when errors occur.23,24 As the prognosis of patients with meningeal disease has not changed for 3 decades,2 any therapy that reduces pain, time, and labor for both patients and treating physicians without a deleterious effect on outcome should be considered as standard therapy. As improved systemic therapy has ironically resulted in greater numbers of patients with leptomeningeal disease, DepoCyt should also be considered in a trial of CNS prophylaxis in patients with ARL and others at high risk of meningeal relapse.

**References**

4. Kim S, Kim DJ, Geyer MA, Howell SB. Multiviscu-
sular liposomas containing 1-beta-D-arabinino-
uronic acid and sirohydrochlorine for slow-release intrath-
5. Murry DJ, Blaney SM. Clinical pharmacology of
encapsulated sustained-release cytarabine. Ann
DG. Cytotoxic arabinoside cerebrospinal fluid ki-
FM, Poplack DG. Prolongation of drug exposure in cerebrospinal fluid by encapsulation into Depo-
Pharmacokinetics of intralumbral DTC-101 for the treat-
ment of leptomeningeal metastases. Arch
9. Glantz MJ, LaFollette S, Jaecelle KA, et al. Ran-
tomized trial of a slow-release versus a standard
formulation of cytarabine for the intrathecal treat-
1999;17:3110-3116.
randomized control trial comparing intrathcal sustained-release cytarabine (DepoCyt) to intra-
theal methotrexate in patients with neoplastic
1999;5:3394-3402.
11. Ferle BF, Glantz MJ, Jaecelle KA, Chamberlain
MC, Mackowick JF. Quality-of-life-adjusted sur-
valival comparison of sustained-release cytosine
arabinoside versus intrathcal methotrexate for
ravement of solid tumor neoplastic meningitis.
Cancer. 2003;97:3053-3060.
Limited patient adherence to highly active antire-
roviral therapy for HIV-1 infection in an observa-
tional cohort study. Arch Intern Med. 2001;161:
13. Osterberg L, Blaschke T. Adherence to medica-
Bower M. Leptomeningeal disease in AIDS-re-
lated non-Hodgkin’s lymphoma. AIDS. 2003;17:
861-865.
DB, Newlands ES. A weekly alternating chem-
otherapy regimen with low toxicity for the treat-
ment of aggressive lymphoma. Cancer Chemother
BG. Weekly alternating combination chemo-
otherapy for good prognosis AIDS-related lym-
inhibitors potentiate chemotherapy-induced neu-
18. Yeni PG, Hammer SM, Carpenter CG, et al. Anti-
retroviral treatment for adult HIV infection in
2002: updated recommendations of the Interna-
tional AIDS Society-USA Panel. JAMA. 2002;288:
222-230.
19. Ickovics JR, Meade CS. Adherence to HAART
among patients with HIV: breakthroughs and bar-
20. Kuo AH, Yataganas X, Galicich JH, Fried J, Clarkson
BD. Proliferative kinetics of central nervous system
studies and distribution dynamics of retroviral
stores following intrathecal administration of retro-
22. Greenfield JP, Bilsky MH. Neurosurgical interven-
tions for leptomeningeal tumor. Cancer Treat
23. Seale JR. Not again! Erroroneous intrathecal injec-
tion results from a problem with protocols. BMJ.
2001;322:548.
24. Dyer C. Doctor’s manslaughter trial halted owing
to defendant’s health. BMJ. 2003;327:123.

To the editor:

Pathology of “Berkeley” sickle-cell mice
includes gallstones and priapism

We appreciate the histopathologic survey of “Berkeley” transgenic sickle-cell mice by Manci and colleagues,1 and we have similar results in a larger range of ages (2 to 23 months) in another subcolony of these mice originally from Drs Chris Pastzy and Mohandas Narla. We also concur that the hemizygote mice are poor models for human sickle trait.2 However, we would like to add 2 additional similarities between these mice and human sickle cell disease that may have relevance to pathophysiology of sickle
cell disease.

While Manci et al found no gallstones, we consistently see a 20% to 30% incidence of pigmented gallstones in examining nearly 100 of these mice. Photomicrographs (see figure) were visualized using an Olympus BX51 microscope (Olympus, Melville, NY) equipped with UPlan Apop 4 ×/0.16 and PlanApo 1.25 × 0.04 objective lenses. Images were captured with an Olympus DP70 camera, and were formatted using Adobe Photoshop software (Adobe Systems, San Jose, CA). Affected mice typically have a
dilated gallbladder containing a single large stone and several smaller ones. Some gallbladders with gallstones are hyperplastic (Figure 1B), but none have histologic signs of cholecystitis or biliary duct obstruction, and we conclude that these gallstones are asymptomatic. The youngest mouse with pigmented gallstones was 6 weeks old. All mice exclusively expressing human sickle
hemoglobin have elevated serum total bilirubin (13 ± 1 µM/L; mean and SEM, n = 16). This is another manifestation of human sickle-cell disease in the mouse model, and it correlates with the high-grade hemolysis in these mice. The only other mice with pigmented gallstones are those with spherocytosis due to the nb/nb mutation, manifesting gallstones after 6 months of age.3,4 Dogs, prairie dogs, and guinea pigs also form pigmented stones.5

Pigment gallstones in “Berkeley” transgenic sickle cell mice. H&E. (A) Stones in a dilated gallbladder; original magnification, × 12.5. (B) Stones in a hyperplastic
gallbladder; original magnification, × 40.
The management of meningeal lymphoma in patients with HIV in the era of HAART: intrathecal depot cytarabine is effective and safe

Danish Mazhar, Justin Stebbing, Rachel Lewis, Mark Nelson, Brian G. Gazzard and Mark Bower