

Editorial

Intrathecal Depot Cytarabine Therapy: A Welcome Addition to a Limited Armamentarium

W. Archie Bleyer¹

The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

The LMD² of a systemic malignancy remains one of the greatest treatment challenges in cancer medicine (1). Few patients with this complication survive for more than a few months, and this outcome has not changed substantially over the past 20–30 years, despite the progress made in controlling cancer at most other sites in the body. Thus, any advance in the treatment of LMD, especially a modality shown to be effective in a randomized, controlled trial, is truly welcome.

Such is the case for the IT SR ara-C described by Glantz *et al.* (2) in this issue of *Clinical Cancer Research*. The ara-C used by these investigators was encapsulated in a multivesicular liposome preparation named DepoFoam, and the product is known as DTC-101 and DepoCyt (3, 4). This encapsulation of the drug in lipid drastically changes the pharmacokinetics of the free ara-C released by IT SR ara-C in CSF, such that the mean elimination $t_{1/2}$ of the depot formulation of free ara-C in CSF is 130–277 h (5), *versus* 3.4 h for native ara-C (Fig. 1; Ref. 6). Furthermore, the cytotoxic concentrations of the SR formulation of the ara-C in CSF are maintained for as long as 14 days or more, depending on the target cell threshold concentration that is cytotoxic. For human lymphoblasts, this concentration is generally thought to be 5 μM , such that the threshold for native ara-C is exceeded for only 1 day or so (Fig. 1). Solid tumors such as carcinoma are thought to have a higher threshold, perhaps 1 or 2 logs higher, but this has not been well characterized.

For IT therapy, MTX has been regarded as a better drug than ara-C, in part because it provides a longer exposure in the CSF and penetrates more deeply into the meninges and CNS parenchyma. Specifically, laboratory studies have shown that ara-C diffuses only a few millimeters into the brain parenchyma, regardless of the time or concentration of ara-C in CSF (7). MTX, on the other hand, penetrates more deeply (as a function of the distance from the ependyma), and the depth increases with higher CSF concentrations and longer exposures to the drug in the CSF.

Prolonged exposure to cytotoxic concentrations of antineoplastic agents such as MTX and ara-C often results in cell kill in

patients with LMD, whereas a short exposure to the same concentrations does not. However, the repeated intra-CSF administrations necessary to accomplish this obviously pose a difficulty, especially when lumbar punctures are required to deliver the agent. To permit repeated intra-CSF administration without the need for repeated lumbar punctures, an Ommaya reservoir is usually implanted with the tip of the cannula inserted into a lateral. However, this requires anesthesia, surgery, and postoperative recovery, and it also risks CNS infection. Nonetheless, this approach has been successful in the treatment of meningeal leukemia (8, 9) or can at least be palliative in patients with solid tumors.

The leptomeninges and CSF pose a special cytotoxic problem for the oncologist. On one hand, the CSF concentrations of any agent are much higher after intra-CSF injection than are the plasma levels that can be achieved with the systemic administration of much higher doses of the drug. For example, to match the CSF concentration achieved by an IT dose of 12 mg, the i.v. dosage of MTX must be 33,600 mg/m² over 24 h, and even then the peak CSF concentrations are a log or more higher with the IT dose (10). In addition, the removal of agents such as MTX and ara-C from the CSF is much slower than that from the systemic compartment. Thus, agents that are ineffective against non-CNS tumors after systemic administration may be effective against LMD and tumor cells elsewhere within the CNS after IT administration. For this reason, drugs that show no detectable antineoplastic activity in standard Phase I or II clinical trials may be rejected on the basis of current findings but may actually be effective against human LMD under other testing conditions.

An additional problem in the treatment of LMD is that malignant cells within the CSF and meninges proliferate very slowly. Leukemic cells, for example have markedly slower cytotoxic kinetics in the CSF and meninges than they do in blood or bone marrow. This has been confirmed by the tritiated uridine labeling index of leukemic cells in bone marrow, blood, and CSF, which was found to be 31.5%, 14.0%, and 1.5%, respectively, and the mitotic index, which was found to be 1.1%, 0.02%, and 0.01%, respectively (11). In another study, CSF blasts were found to have thymidine labeling indices of less than 2%, and both CSF and meningeal leukemic cells had mitotic indices of less than 0.02% (12). In patients with meningeal leukemia, the growth fraction has been estimated on the basis of repeated intraventricular injections of tritiated thymidine via an Ommaya reservoir; after 10 days of continuous exposure to the radiolabeled nucleoside, only 21–55% of the cells in the CSF were labeled (12). These observations indicate that the eradication of LMD in patients with cancer will require extraordinarily long exposures to cytotoxic concentrations of the antineoplastic agent, especially if it is a cell cycle active agent. Thus, despite the pharmacological advantage of IT administration of an antineoplastic agent in patients with LMD *versus* systemic administration, the cytotoxic kinetics of LMD can nullify this advantage.

Received 8/13/99; accepted 8/18/99.

¹To whom requests for reprints should be addressed, at Division of Pediatrics-87, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 792-6603; Fax: (713) 745-1549; E-mail: ableyer@mdanderson.org.

²The abbreviations used are: LMD, leptomeningeal dissemination; CSF, cerebrospinal fluid; MTX, methotrexate; CNS, central nervous system; RR, relative risk; SR, sustained release; IT, intrathecal; ara-C, 1- β -D-arabinofuranosylcytosine, cytarabine.

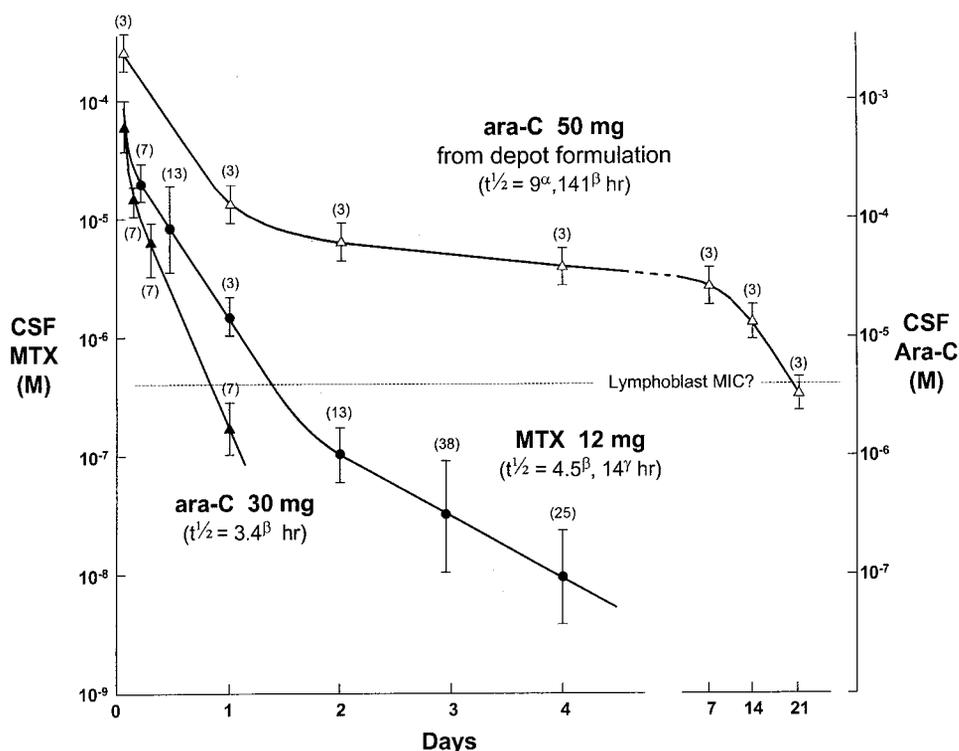


Fig. 1 CSF MTX and ara-C concentrations in patients treated with 12 and 30 mg, respectively. The MTX data were derived from Bleyer (14), the ara-C data were derived from Zimm *et al.* (6), and the depot ara-C data were derived from Kim *et al.* (4). The depot data were for free ara-C released from SR multivesicular liposomes. The ara-C levels were measured in ventricular CSF after intraventricular injection via an Ommaya reservoir, and the MTX levels were measured in lumbar CSF after intralumbar administration. Vertical bars, SEs for ara-C and SDs for MTX. The mean inhibitory concentration (MIC) for human lymphoblasts for MTX was derived from Hyrniuk and Bertino (15), and the mean inhibitory concentration for human lymphoblasts for ara-C was derived from Ho and Frei (16).

The neurotoxicity of prolonged exposure to an antineoplastic agent also limits use of this method, and this applies to many agents. Fortunately, neither IT ara-C nor IT MTX is associated with a significant toxicity rate according to the concentration \times time method, at least not at the doses and durations that have been evaluated using this method (MTX, 2 mg daily for up to 8 days; ara-C, 5–15 mg daily for up to 4 days). The repeated administration of IT SR ara-C every 2 weeks for 2 months and then monthly thereafter also appears to be tolerable, according to the report in this issue of *Clinical Cancer Research* (2). The primary toxicity was neurological, as expected, and was mostly attributable to chemical arachnoiditis.

Nausea and vomiting after IT SR ara-C were infrequent, with grade 3 or 4 levels of this toxicity occurring in only 3 of 29 patients and 3 of 102 cycles. All but 2 of 29 patients received the drug via the intraventricular route. This low rate of nausea and vomiting after intraventricular administration is surprising because the intraventricular injection of native ara-C induces a high rate of vomiting (>90% with doses >15 mg) due to a direct effect of the agent on the periventricular emetic centers in the brain stem. In contrast, vomiting rarely occurs with intralumbar ara-C, even up to doses of 100 mg.

In the randomized trial reported by Glantz *et al.* (2), IT SR ara-C at a dosage of 50 mg every 2–4 weeks for up to six times was compared with IT MTX at a dosage of 12 mg twice weekly for up to 16 times. MTX was chosen for the control regimen because it is the standard agent used for IT therapy and, as implied in Fig. 1, is more effective dose for dose than conventional ara-C.

A conservative interpretation of the trial outcome is that IT

SR ara-C is equally effective and no more toxic than IT MTX given in the schedules used. However, the real advantage of IT SR ara-C is that fewer doses were needed to achieve the same effect as IT MTX. Nevertheless, if this is the only conclusion, the true value of IT SR ara-C may be somewhat limited by the nature of the trial. In particular, to prevent systemic toxicity from IT MTX, leucovorin was given to all patients treated with IT MTX, starting 24 h after the MTX injection and repeated every 6 h for six times. This schedule of leucovorin is aggressive, and although it is very protective against systemic exposure, it may also reduce the cytotoxicity of malignant cells within the CNS. The dosage of leucovorin is also important because the primary metabolite of leucovorin, 5-methyltetrahydrofolate, is actively transported into the CSF, reaches concentrations 2–3 times higher in CSF than in plasma, and can readily rescue malignant cells in the CNS. A more optimal balance between systemic protection and maximum CNS benefit would have been achieved either by delaying the onset of leucovorin rescue until 36–42 h after the administration of IT MTX or by giving fewer doses.

Another limitation of the comparison is that dexamethasone was routinely given for 5 days during each treatment cycle. Because hydrocortisone inhibits MTX uptake by malignant cells (13), it is quite possible that the effectiveness of IT MTX was further compromised as a result.

A more liberal conclusion to be drawn from this study is that IT SR ara-C administered every 2–4 weeks is more effective than IT MTX administered twice weekly. Indeed, this was suggested in this trial by the univariate and multivariate analyses demonstrating that progression-free survival was significantly

greater in the patients receiving IT SR ara-C than in patients receiving IT MTX (RR = 0.44 and $P = 0.006$ and RR = 0.34 and $P = 0.002$, respectively). An additional benefit of IT SR ara-C was that there was a greater time to neurological progression in the IT SR ara-C group than in the IT MTX group (median 58 days *versus* 30 days, $P = 0.007$). It is also possible that the SR formulation of ara-C penetrates more deeply as a function of the distance from the ependyma and that disease within the brain parenchyma can be treated more effectively with SR ara-C than with the native drug. The observation that patients with a history of intraparenchymal disease had a better outcome (RR = 0.14; $P < 0.001$) in the reported trial suggests that both IT MTX and IT SR ara-C can be effective against parenchymal tumors. Whether IT SR ara-C is *more* effective in this setting was either not analyzed, or the data did not support this conclusion.

Regardless of the interpretation, IT SR ara-C has a distinct advantage over both MTX and native ara-C in its frequency of administration, and it clearly offers a significant alternative to available IT agents. Our limited armamentarium of IT agents is now expanded with a formulation that has successfully taught an old dog a new trick. For patients with LMD, IT SR ara-C is a *bona fide* advance.

REFERENCES

1. Bleyer, W. A., and Byrne, T. N. Leptomeningeal cancer in leukemia and solid tumors. *Curr. Probl. Cancer*, 12: 181–238, 1988.
2. Glantz, M. J., Jaeckle, K. A., Chamberlain, M. D., Phuphanich, S., Recht, L., Swennen, L. J., Maria, B., LaFollette, S., Schumann, G. B., Cole, B. F., and Howell, S. B. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin. Cancer Res.*, 5: 3394–3402, 1999.
3. Kim, S., Kim, D. J., Geyer, M. A., and Howell, S. B. Multivesicular liposomes containing 1-B-D-arabinofuranosylcytosine for slow-release intrathecal therapy. *Cancer Res.*, 47: 3935–3937, 1987.
4. Kim, S., Khatibi, S., Howell, S. B., McCully, C., Balis, F. M., and Poplack, D. G. Prolongation of drug exposure in cerebrospinal fluid by encapsulation into DepoFoam. *Cancer Res.*, 53: 1596–1598, 1993.
5. Chamberlain, M. C., Kormanik, P., Howell, S. B., and Kim, S. Pharmacokinetics of intralumbar DTC 101 for the treatment of leptomeningeal metastases. *Arch. Neurol.*, 52: 912–917, 1995.
6. Zimm, S., Collins, J. M., Miser, J., Chatterji, D., and Poplack, D. G. 1-β-D-Arabinofuranosylcytosine cerebrospinal fluid kinetics. *Clin. Pharmacol. Ther.*, 35: 826–830, 1984.
7. Blasberg, R., Fenstermacher, J., Levin, V., and Patlack, C. Intrathecal chemotherapy: brain tissue profiles after ventriculocisternal perfusion. *J. Pharmacol. Exp. Ther.*, 195: 73–83, 1975.
8. Bleyer, W. A., Poplack, D. G., and Simon, R. M. “Concentration × time” methotrexate via a subcutaneous reservoir: a less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. *Blood*, 51: 835–842, 1978.
9. Bleyer, W. A., and Poplack, D. G. Intraventricular *versus* intralumbar methotrexate for central-nervous-system leukemia: prolonged remission with the Ommaya reservoir. *Medical Pediatr. Oncol.*, 6: 207–213, 1979.
10. Poplack, D., Reaman, G., Bleyer, A., Miser, J., Feusner, J., Wesley, F., and Hammond, D. Central nervous system preventive therapy with high dose methotrexate in acute lymphoblastic leukemia. *Proc. Am. Soc. Clin. Oncol.*, 3: 204, 1984.
11. Tsuchiya, J., Moteki, M., Shimano, S., Shinonome, S., Suda, T., Omine, M., and Maekawa, T. Proliferation kinetics of the leukemic cells in meningeal leukemia. *Cancer (Phila.)*, 42: 1255–1262, 1978.
12. Kuo, A. H., Yataganas, X., Galalich, J. H., Fried, J., and Clarkson, B. D. Proliferation kinetics of central nervous system leukemia. *Cancer (Phila.)*, 36: 232–239, 1975.
13. Bender, R. A., Bleyer, W. A., Frisby, S. A., and Oliverio, V. T. Alteration of methotrexate uptake in human leukemia cells by other drugs. *Cancer Res.*, 35: 1305–1308, 1975.
14. Bleyer, W. A. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat. Rev.*, 4: 87–101, 1977.
15. Hymniuk, W. M., and Bertino, J. R. Treatment of leukemia with large doses of methotrexate and folic acid: clinical-biochemical correlates. *J. Clin. Investig.*, 48: 2140–2155, 1969.
16. Ho, D. H. W., and Frei, E. Clinical pharmacology of 1-β-D-arabino-furanosyl cytosine. *Clin. Pharmacol. Ther.*, 12: 944–954, 1971.

Clinical Cancer Research

Intrathecal Depot Cytarabine Therapy: A Welcome Addition to a Limited Armamentarium

W. Archie Bleyer

Clin Cancer Res 1999;5:3349-3351.

Updated version Access the most recent version of this article at:
<http://clincancerres.aacrjournals.org/content/5/11/3349>

Cited articles This article cites 14 articles, 6 of which you can access for free at:
<http://clincancerres.aacrjournals.org/content/5/11/3349.full#ref-list-1>

Citing articles This article has been cited by 3 HighWire-hosted articles. Access the articles at:
<http://clincancerres.aacrjournals.org/content/5/11/3349.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://clincancerres.aacrjournals.org/content/5/11/3349>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.