Liposomal cytarabine (DepoCyte®) for the treatment of neoplastic meningitis

Antonio Rueda Domínguez, David Olmos Hidalgo, Ruth Viciana Garrido and Esperanza Torres Sánchez

Servicio de Oncología Clínica. Hospital Universitario Virgen de la Victoria. Málaga. Spain.

Neoplastic meningitis is a feared complication in cancer patients, the median survival ranging from some weeks to a few months. Management is palliative and aims to provide symptoms relief while delaying neurological deterioration.

Intrathecal methotrexate and/or cytarabine is the most widely used treatment in such clinical situations. These drugs are administered 2 or 3 times a week – a circumstance that is both bothersome for the patient and time-costly for the medical personnel. Liposomal cytarabine is a sustained-release cytarabine formulation specifically developed for the treatment of neoplastic meningitis. Its administration on a twice-weekly basis ensures sustained cytotoxic drug concentrations in cerebrospinal fluid.

Controlled clinical trials have shown liposomal cytarabine to be equally or more effective than the classical treatment for neoplastic meningitis. In lymphomatous meningitis, liposomal cytarabine offers superior response rates, improved patient quality of life, and a prolongation of the time to neurological progression. When the cause of meningitis is a solid tumor, liposomal cytarabine prolongs the time to neurological progression and improves quality of life.

These observations indicate that DepoCyte®, is a convenient treatment for patients with neoplastic meningitis, due to its efficacy and easy of administration characteristics.

Key words: neoplastic meningitis, treatment, liposomal cytarabine.

Rueda Domínguez A, Olmos Hidalgo D, Viciana Garrido R, Torres Sánchez E. Liposomal cytarabine (DepoCyte®) for the treatment of neoplastic meningitis. Clin Transl Oncol. 2005;7(6):232-8.

Correspondence: Antonio Rueda Domínguez.
Servicio de Oncología Médica.
Hospital Clínico Universitario.
Campus de Teatinos s/n.
29010 Málaga.
E-mail: ruedom@yahoo.com

Received 17 September 2004; Revised 7 February 2005; Accepted 9 February 2005.

INTRODUCTION

Neoplastic meningitis occurs when cancer cells metastasize to the meninges and cerebrospinal fluid (CSF). This phenomenon complicates the course of patients with systemic lymphoma in 4%-25% of cases[1], and manifests in symptomatic form in at least 5%-8% of patients with solid tumors (mainly melanoma, breast and lung cancer)[2]. Neoplastic meningitis is a feared and devastating complication that clinically manifests in the form of signs and symptoms that reflect tumor invasion of the nerve roots that penetrate the subarachnoid space. From the time of diagnosis, most patients suffer rapid neurological deterioration, with a median survival of only a few weeks or months. The purpose of treatment in such situations is to palliate the symptoms and delay the progressive neurological impairment[3,4].

The administration of chemotherapeutic agents via the intravenous route offers a very limited therapeutic effect in the management of neoplastic meningitis, due to the limited capacity of most such drugs to cross the blood-brain barrier. As a result, direct drug administration into the CSF compartment is necessary in such patients. The standard treatment for neoplastic meningitis comprises irradiation of the disease locations that are visible in the radiological imaging studies, together with the intrathecal (IT) administration of chemotherapy.

Three drugs are available for IT administration: methotrexate (MTX), cytarabine (ara-C) and thiotepa. However, established IT therapy poses a series of problems. Firstly, the half-life of these drugs within the CSF is very short – as a result of which good diffusion throughout the CSF compartment is not achieved, and certain areas show only low exposure to treatment. Secondly, since the drug concentrations in CSF quickly fall to below therapeutic levels, the medication must be administered 2-3 times a week – and this implies the need for 2-3 painful lumbar injections weekly, or the placement of a ventricular reservoir. These procedures are bothersome for the patient and very time-consuming for the medical personnel. Any effective treatment offering the possibility of less frequent administration therefore would constitute an advance in patient management.

The results of neoplastic meningitis treatment are not good. In the case of lymphomatous meningitis, no

controlled studies or prospective phase II trials have been conducted to evaluate the efficacy of treatment. There are only two studies reporting the results of two prospectively treated patient series: one in HIV-negative subjects[5], and the other in patients with HIV-related lymphoma[6]. The median time to neurological progression was 60 days in both studies, with a median survival time of 10 months and only 4 months in patients without and with HIV infection, respectively.

Two comparative studies and a number of prospective trials have evaluated the treatment of neoplastic meningitis caused by solid tumors[4,7-9]. In the controlled study conducted by Grossman[8], 75% of the 28 randomized patients were received MTX or thiotepa showing neurological progression on day 56, and the median survival time in the MTX group was 111 days. In the study published by Hitchins[9], the median survival time of the patients administered MTX was 84 days.

The above data point out the urgent need for new therapeutic agents that are both more effective and easier to administer to patients with this neoplastic involvement.

LIPOSOMAL CYTARABINE (DepoCyte®): DESCRIPTION AND CLINICAL PHARMACOLOGY

Cytarabine is a cell cycle-specific antimetabolite that only kills tumor cells upon entering the S-phase of the cell cycle. In this way, its cytotoxicity is dependent upon the dose administered and the duration of exposure. Maximum tumor cell destruction is achieved when effective drug concentrations are maintained in the tumor cell environment for prolonged periods of time[10]. However, due to the short half-life of the drug (3.4 hours)[11], the injection of free cytarabine into the CSF compartment offers cytotoxic concentrations for fewer than 24 hours. Since the drug is rapidly cleared from CSF in relation to the flow dynamics of the latter, optimum cytarabine distribution to both extremes of the neuraxis is not achieved – even when administering 2-3 injections per week.

Liposomal cytarabine is a liposome-based, sustained-release formulation specifically developed for the treatment of neoplastic meningitis. In this formulation, cytarabine is encapsulated in the aqueous compartments of a matrix composed of phospholipids, triglycerides and cholesterol. The spherical particles (measuring about 20 µm in diameter) are mixed with saline solution to yield a suspension with the consistency and appearance of skimmed milk, and which can easily be injected with a 28G needle. The particles remain stable when stored at 2-8ºC; upon injection into the CSF compartment, they spread throughout the neural tube and slowly release the active drug substance. The particles gradually disintegrate and disappear within the CSF, and their lipid constituents

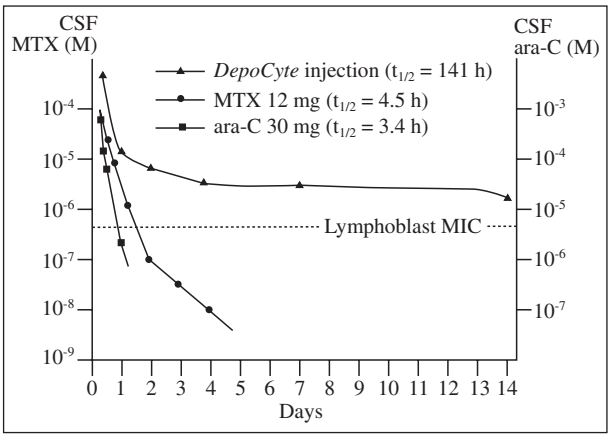

Fig. 1. Half life of free cytarabine in CSF after the administration of a single DepoCyte® dose.

are incorporated to the normal body metabolic pathways[12].

In the phase I study[13], the area under the concentration-time curve (AUC) of free and encapsulated cytarabine following the intraventricular administration of liposomal cytarabine was seen to increase linearly with the dose. As can be seen in figure 1, the half-life of the drug in CSF following the administration of a free cytarabine dose was 3.4 hours. In comparison, after administering 50 mg of liposomal cytarabine (the recommended dose for phase II studies), the concentration of free cytarabine in CSF decreased bi-exponentially, with an initial half-life of 9.4 hours and a terminal half-life of 141 ± 23 hours. In this way, free cytarabine concentrations of > 0.02 µg/ml where maintained in the lumbar sac and lateral ventricles for more than 14 days. This concentration is cytotoxic for practically all tumor cells when prolonged exposure to the drug is maintained[14].

A single injection of 50 mg of liposomal cytarabine maintains cytotoxic drug concentrations in CSF for over 14 days in almost all patients, with adequate cytarabine distribution throughout the CSF compartment[15]. As can be seen in the compartmental representation in figure 2, while cytarabine is hardly

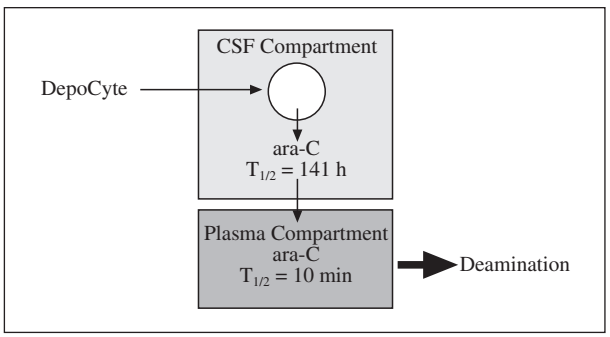

Fig. 2. Biodistribution of free ara-C after the administration of a single DepoCyte® dose.

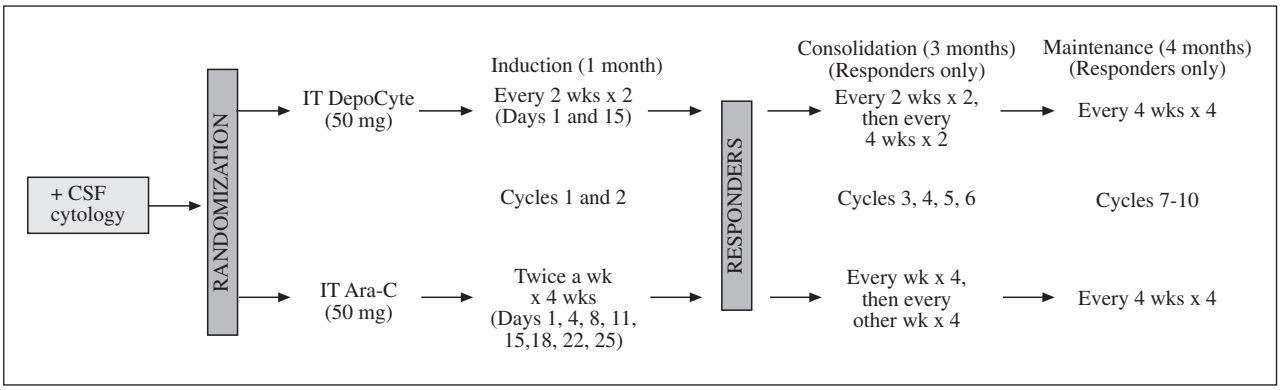

Fig. 3. Lymphomatous meningitis phase III study.

metabolized in CSF and most of the drug eventually penetrates the systemic circulation, the degree of dilution in blood and the rapidity of liver metabolization ensure that cytarabine is not detected in plasma following IT injection of the drug. Thus, effective IT therapy can be achieved with a single injection every two weeks, with no systemic toxic effects and without having to worry about whether concomitant systemic chemotherapy will be affected.

CLINICAL STUDIES WITH LIPOSOMAL CYTARABINE

Intrathecal therapy phase I study

The phase I study carried out in the University of California (San Diego Cancer Center) included 19 patients administered 1-8 cycles of liposomal cytarabine at doses of 12.5 to 125 mg[16]. The intraventricular or intrathecal route was used. The most frequent adverse effects were headache, nausea, vomiting and fever. All these problems proved reversible in under 7 days. It should be pointed out that the recorded adverse effects were no different from those expected for intrathecal chemotherapy. The dose-limiting toxic effect was encephalopathy, at a dose of 125 mg. The maximum tolerated dose was 75 mg, as a result of which the next lower dosage (50 mg) was recommended for testing in future clinical trials.

It should be pointed out that CSF cytology showed negative conversion in 10 out of 16 patients evaluable to the effects of treatment response (63%) – including 3 out of 6 patients (50%) with lymphomatous meningitis[16].

Phase III study of the treatment lymphomatous meningitis

This study comprised an open, randomized multicentre and parallel group design in which the patients received liposomal cytarabine or free cytarabine intrathecally. Figure 3 provides a schematic representation of the study design[17].

Subjects were required to present histologically confirmed lymphoma, with positive CSF cytology and a Karnovsky index $>$ 50%. Concomitant systemic chemotherapy was provided for the extrameningeal disease – with the exception of high doses of MTX, cytarabine or thiotepa. Patients with symptomatic and radiologically visible CNS disease were allowed to receive local radiotherapy during the induction period, though concomitant craniospinal or holocranial irradiation was not permitted. Unless already receiving the drug, all patients were administered 4 mg of dexamethasone intravenously or via the oral route twice a day on days 1 to 5 of each treatment cycle.

Although the initial aim was to include 20 patients in each treatment arm, following inclusion of the first 28 subjects a large difference in response was noted between the two arms; the interruption of further patient inclusion was therefore decided. The baseline characteristics of the patients were balanced in terms of factors of possible prognostic importance for lymphomatous meningitis, such as age, sex, race, the presence or absence of AIDS, and the Karnofsky index.

The study endpoints were the cytological response rate, time to neurological progression, and the survival time due to meningeal disease. Treatment response was defined by the clearance of lymphomatous cells in CSF, in the absence of progression of the neurological symptoms.

71% of the patients treated with liposomal cytarabine showed cytological response, versus only 14% of those administered free cytarabine ($p = 0.006$). There were no differences in response to liposomal cytarabine between the patients who received systemic chemotherapy and those who did not. A tendency towards longer time to neurological progression was recorded among the patients treated with liposomal cytarabine. The median time to neurological progression was 78.5 and 42 days, respectively. The number of patients included in the trial did not allow the de-

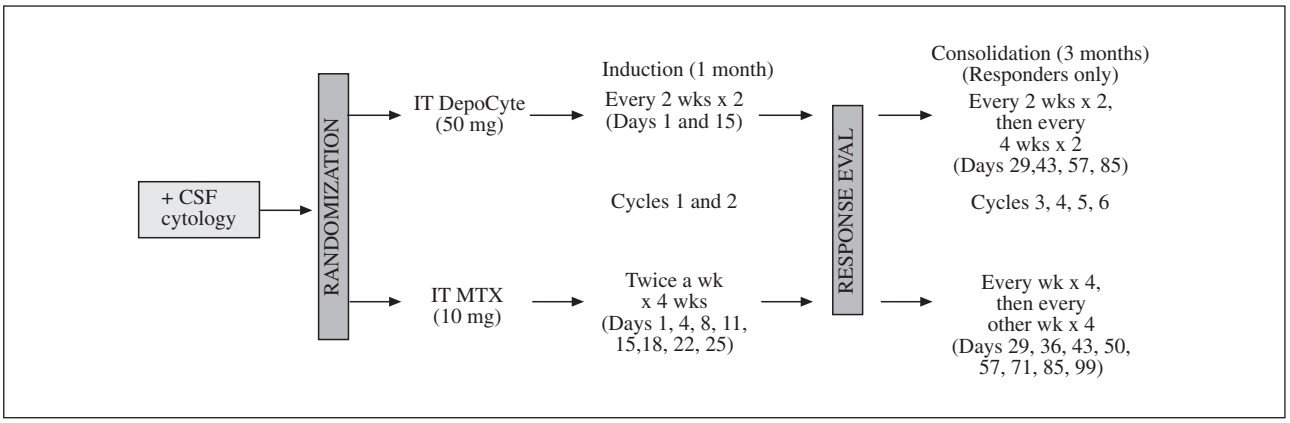

Fig. 4. Meningitis produced by solid tumors. Phase III study.

tection of differences in global survival or meningeal progression-free survival.

A quality of life analysis was conducted in both arms of the study, based on a Q-TWiST scale (Quality adjusted Time Without Symptoms or Toxicity). The patients treated with liposomal cytarabine showed a 5.9-fold increase in disease progression- and treatment adverse effect-free survival versus the subjects administered free cytarabine. This difference was not statistically significant, however – probably because of the small size of the sample.

This is the only controlled trial for any drug in patients with lymphomatous meningitis to date. The inclusion of only 28 patients over a period of 40 months reflects the difficulty of conducting controlled studies in such infrequent and difficult clinical situations. Nevertheless, the conclusions drawn from the trial in no way lose validness as a result.

Phase III study of the treatment of neoplastic meningitis produced by solid tumors

This open, randomized multicenter and parallel group study was made to determine the efficacy and safety of liposomal cytarabine compared with standard IT therapy with methotrexate for the treatment of neoplastic meningitis secondary to cytologically demonstrated solid tumors. The design was identical to that used in lymphomatous meningitis - with the exception that there was no maintenance treatment (fig. 4)[18].

The patients were required to have solid tumor with histological confirmation and cytologically demonstrated meningeal involvement, a Karnovsky index > 50% and a live expectancy of at least two months. The patients with symptomatic and radiologically visible CNS disease could receive local radiotherapy during induction, but concomitant craniospinal or holocranial irradiation was not permitted. Standard supportive therapy was allowed, including oral or intravenous corticoids.

The trial objectives and methodology – including the analysis of patient quality of life – were the same as in the case of the study of lymphomatous meningitis (see above).

A total of 61 patients were included (31 in the liposomal cytarabine arm and 30 in the MTX group) – this represents the largest comparative trial to date in the context of this particular clinical situation. The two study arms were well balanced in relation to the known prognostic factors.

There were no differences in the cytological response rates obtained. 26% of patients treated with liposomal cytarabine responded, versus 20% of those treated with MTX. Figure 5 shows that treatment with liposomal cytarabine offered a statistically significant prolongation of time to neurological progression ($p = 0.0068$). The criteria of neurological progression were easily identified by the main investigator as well as for the patient, and included the appearance of walking difficulties, vision loss, or the development of new cranial or spinal nerve paralysis. It is important to highlight that the prolongation of time to neurological progression is a principal objective of palliative therapy in this particular clinical situation.

The median survival time was 101 versus 78 days in favor of liposomal cytarabine (nonsignificant difference). Survival time at 6 months (41% versus 17%) and at 12 months (17% versus 8%) likewise favored the group treated with liposomal cytarabine. The analysis of quality of live based on the Q-TWiST method showed liposomal cytarabine to yield a 4-fold increase in time without symptoms due to disease progression or treatment toxicity ($p<0.05$).

The results of this study show that liposomal cytarabine is at least as effective as MTX, though is comparatively superior in terms of the duration of treatment effect. On the other hand, it is more convenient, since it requires only one-quarter as many visits to the Oncological Day Hospital – this represents a clear bene-

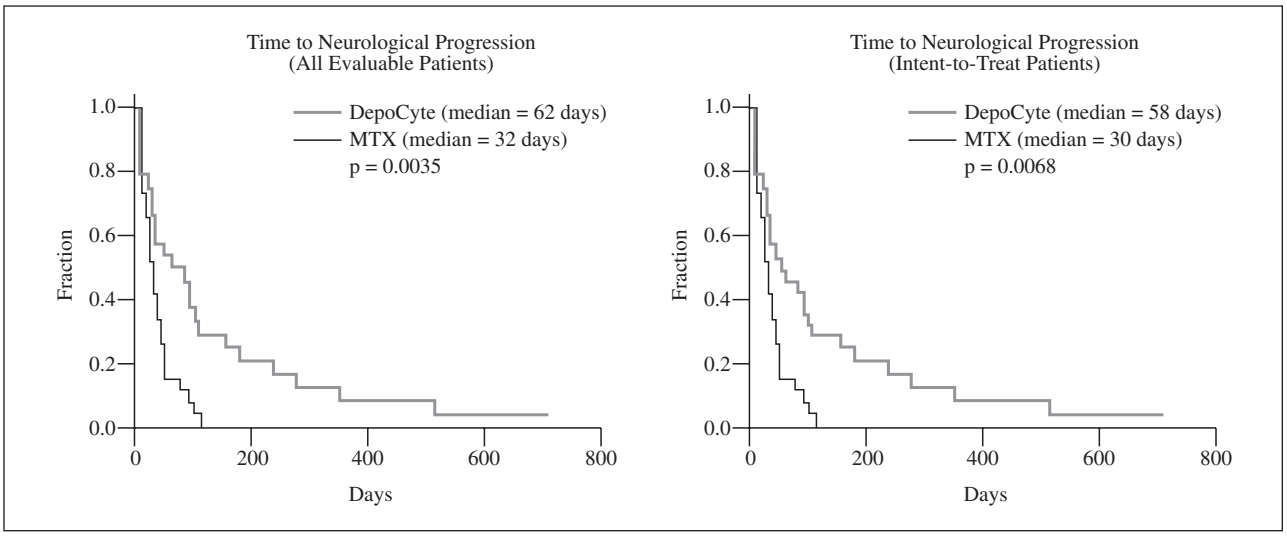

Fig. 5. Time to neurological progression in patients with solid tumors.

fit for the patients, who often have mobility problems secondary to the neurological impairment.

After the presentation of this study there have been two non-comparative prospective studies that have evaluated the efficacy of liposomal cytarabine in patients with neoplastic meningitis secondary to solid tumors (confirmed or otherwise)[19,20]. The patients without cytological confirmation presented sufficient neurological or radiological evidence to diagnose neoplastic meningitis. In this less selected population the response rate was 21%-27%, and the median survival time 88 and 95 days, respectively[19, 20].

Cytarabine is rarely used for the treatment of solid tumors, since the doses and exposure times required for most histological types would be non-tolerable for the bone marrow. However, the drug levels reached in CSF when administering liposomal cytarabine intrathecally is cytotoxic for a great variety of solid tumors. Liposomal cytarabine is active in neoplastic meningitis caused by most solid tumors; this activity has been analyzed in the patients with solid tumors and neoplastic meningitis included in the different trials conducted during development of the product[16,18-20]. The cytological response rate recorded for the different histological types was as follows: breast cancer 39%; non-microcytic lung carcinoma 28%; melanoma 18%; NOS adenocarcinoma 14%; glioblastoma 20%; neuroectodermal tumors 71%; medulloblastoma 75%; carcinoma of indeterminate origin 67%; microcytic lung carcinoma 0%.

LIPOSOMAL CYTARABINE (DepoCyte®): TOXICITY

The analysis of adverse effects in patients with neoplastic meningitis should take into account that most such individuals present neurological manifestations secondary to the tumor process and which can be mistaken for toxic effects of treatment. The analysis of cycle by cycle toxicity in the two comparative studies commented above[17,18] shows that liposomal cytarabine is not more toxic than free cytarabine or MTX when administered via the IT route. The most common adverse effects were headache, nausea, vomiting and arachnoiditis; most of these problems were of grade 1-2 (75%-80%) and of a transient nature – with a good response to symptomatic therapy – and had disappeared at the end of the treatment cycle in which they appeared. In all studies the risk of grade 4 adverse effects is $< 5\%$ in each treatment cycle with any of the three study drugs.

In the analysis of liposomal cytarabine toxicity, a number of aspects should be taken into account. Firstly, there have been no reports of specific liposomal cytarabine toxicity other than that already known for IT chemotherapy. Secondly, no evidence of cumulative toxicity has been observed with liposomal cytarabine. On the other hand, IT therapy with liposomal cytarabine did not influence the toxicity of the systemic therapy provided.

The most significant side effects – headache and arachnoiditis – deserve separate mention. Headache is a complication of all forms of IT therapy, and was the only adverse effect observed in over 10% of cycles in all studies. Headache of certain intensity was more common in patients treated with liposomal cytarabine than in those administered free cytarabine or MTX – this being compatible with the much greater CSF compartment exposure to chemotherapy. Nevertheless, when presented, headache was generally of low intensity and responded adequately to aspirin or paracetamol. Grade 3 headaches were only recorded in 4% of the cycles.

Arachnoiditis can be caused by tumor infiltration of the meninges or by IT drug administration and it is often difficult to distinguish between the two causes. No differences were recorded among the three drugs in terms of the incidence of the complex signs and symptoms included in the algorithm used to define arachnoiditis. In effect, arachnoiditis of any grade was recorded in 20% of the cycles with liposomal cytarabine, in 19% of the cycles with MTX, and in 13% of the cycles with free cytarabine. Arachnoiditis was of grade 3-4 in 6% of the cycles with liposomal cytarabine (versus 3% with MTX and 7% with free cytarabine). No patient had to discontinue the study treatment because of arachnoiditis, and when the latter appeared, it proved transient and did not delay administration of the next cycle. No cumulative risk was recorded on increasing the number of treatment cycles.

CONCLUSIONS

Neoplastic meningitis is a feared and infrequent complication of cancer. Treatment provided for controlling the problem is of limited efficacy – particularly when primary malignancy is a solid tumor.

While liposomal cytarabine is not a new drug, it constitutes a new formulation of a drug substance with a well known pharmacological and toxicity characteristics. Firm pharmacological bases exist for the development of a sustained release formulation of cytarabine, and the expectations generated by the drug have been confirmed by evidence indicating that this novel formulation offers increased activity against neoplastic meningitis – without increasing the side effects of other IT treatments.

The results of the controlled clinical trial comparing DepoCyte®, with free cytarabine as IT treatment for lymphomatous meningitis indicate that the new medication offers an increased response rate, with improved patient quality of life. It also prolongs the time to neurological progression, though statistical significance was not reached because of the limited size of the study sample.

In the case of neoplastic meningitis due to solid tumors, DepoCyte® did not increase the response rate versus that recorded for intrathecal MTX. However, it significantly prolonged the time to neurological progression and improved patient quality of life. The difference in median survival time was not significant, though liposomal cytarabine doubled global survival at 6 and 12 months.

Classical treatment for neoplastic meningitis required 2 or 3 weekly lumbar puncture procedures or the neurosurgical placement of an intraventricular reservoir. This not only implied patient pain and suffering but also required multiple visits to the Oncological Day Hospital. The treatment of neoplastic meningitis with DepoCyte® requires a single administration every two weeks – this is an important benefit for patients with advanced stage cancer.

All these observations indicate that DepoCyte®, is the more convenient treatment for patients with neoplastic meningitis.

The future development of this product should be focused on the prevention of meningeal involvement in neoplastic processes with a high risk of subclinical meningeal spread. The prognostic factors of meningeal relapse are well known in aggressive non-Hodgkin lymphomas[21], but require better definition in the case of solid tumors.

References

1. Herman TS, Hammond N, Jones SE, et al. Involvement of the central nervous system by non-Hodgkin's lymphoma: the Southwest Oncology Group experience. Cancer. 1979;43:390-7.
2. Bleyer WA. Leptomeningeal cancer in leukaemia and solid tumors. Curr Probl Cancer. 1988;12:184-238.
3. Wasserstrom WR, Glass JP, Posner JB, et al. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. Cancer. 1982;49: 759-72.
4. Boogerd W, Hart AAM, Van der Sande JJ, et al. Meningeal carcinomatosis in breast cancer. Cancer. 1991;67: 1685-95.
5. Chamberlain MC, Kormanik PA. Non-AIDS-related lymphomatous meningitis: combined modality therapy. Neurology. 1997;49:1728-31.
6. Chamberlain MC, Dirr L. Involved field radiotherapy and intra-ommaya methotrexate/ara-C in patients with AIDS-related lymphomatous meningitis. J Clin Oncol. 1993;11:1979-84.
7. Giannone L, Greco FA, Hainsworth JD, et al. Combination intaventricular chemotherapy for meningeal neoplasia. J Clin Oncol. 1986;4:68-73.
8. Grossman SA, Finkelstein MD, Ruckdeschek JC, et al. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. J Clin Oncol. 1993;11: 561-9.
9. Hitchins RN, Bell DR, Woods RL, et al. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol. 1987;5:1655-62.
10. Graham FL, Whitmore GF. The effect of 1-beta-D-arabinofuranosylcytosine on growth, viability, and DNA syntesis of mouse L-cells. Cancer Res. 1970;30: 2627-35.
11. Zimm S, Collins JM, Miser J, et al. Cytosine arabinoside cerebrospinalfluid kinetics. Clin Pharmacol Ther. 1984; 35:826-30.
12. Kohn FR, Malkmus SA, Brownson EA, et al. Fate of the predominant phospholipid component of DepoFoam drug delivery matrix after intrathecal administration of sustained-release encapsulated cytarabine in rats. Drugs Delivery. 1998;5:143-51.
13. Chamberlain MC, Kormanik P, Howell SB, Kim S. Pharmacokinetics of intralumbar DTC-101 for the treatment of leptomeningeal metastases. Arch Neurol. 1995;52:912-7.
14. Frei E, Bickers JN, Hewlett JS, et al. Dose schedule and antitumor studies of arabinosyl cytosine (NSSC 63878). Cancer Res. 1969;29:1325-32.

15. Kim S, Chatelut E, Kim JC, et al. Extended CSF citarabine exposure following intrathecal administration of DTC 101. J Clin Oncol. 1993;11:2186-93.
16. Chamberlain MC, Khatibi S, Kim JC, Howell SB, Chatelut E, Kim S. Treatment of leptomenigeal metastasis with intraventicular administration of depot cytarabine (DTC 101). A phase I study. Arch Neurol. 1993;50:261-4.
17. Glantz MJ, Lafollete S, Jaeckle KA, et al. Randomized trial of a slow-release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol. 1999;17:3110-6.
18. Glantz MJ, Jaeckle KA, Chamberlain MC, et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res. 1999;5:3394-402.
19. Jaeckle KA, Phuphanich S, Bent MJ, et al. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. Br J Cancer. 2001;84:157-63.
20. Jaeckle KA, Batchelor T, O´Day SJ, et al. An open label trial of sustsined-release cytarabine (DepoCyt) for the intrathecal treatment of solid tumor neoplastic meningitis. J Neurooncol. 2002;57:231-9.
21. Haioun C, Besson C, Lepage E, et al. Incidence and risk factors of central nervous system relapse in histologically aggressive non-Hodgkin´s lymphoma uniformly treated an receiving intrathecal central nervous system prophylaxis: a GELA study on 974 patients. Groupe d´Etudes des Lymphomes de l´Adulte. Ann Oncol. 2000; 11:685-90.