

Intrathecal Liposomal Cytarabine and Leptomeningeal Medulloblastoma Relapse: A Valuable Therapeutic Option

ANGELA MASTRONUZZI¹, FRANCESCA DEL BUFALO¹, ANNA IACONO²,
DOMITILLA ELENA SECCO¹, ANNALISA SERRA¹, GIOVANNA STEFANIA COLAFATI³,
MARIA ANTONIETTA DE IORIS¹ and TIZIANA CORSETTI²

¹*Division of Hematology/Oncology and Stem Cell Transplantation,*

²*Hospital Pharmacy Unit,*

³*Department of Imaging, Neuro-Radiology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*

Abstract. *Background: Relapsed medulloblastoma (MB) is a highly lethal disease, requiring for new effective treatment strategies. Intrathecal (IT) therapy both for de novo or relapsed brain tumors with meningeal metastasis is rarely used in first line and relapse protocols. Patients and Methods: We report on three cases of children with relapsed MB treated with IT liposomal cytarabine administered after mild sedation every 15 days. Results: The treatment was well-tolerated in all patients, achieving a prolonged progression-free survival (4-11 months) with a good quality of life. Conclusion: This experience suggests the need for a phase II trial in brain embryonal tumors with leptomeningeal metastasis to better evaluate the efficacy of IT liposomal cytarabine.*

Medulloblastoma (MB) is a highly malignant embryonal tumor, accounting for 20% of central nervous system (CNS) tumors in children. Outcomes strongly depend on the histology, biological markers/features and extension of the disease at diagnosis: 5-year event-free survival ranges from 80-85% for localized MB to 40-70% for high-risk disease (1, 2). MB has an aggressive behavior with a high propensity to metastasize *via* the cerebrospinal fluid (CSF) (3). Current standard-of-care in patients with MB involves multimodal treatment including surgery, radiation and chemotherapy, sometimes at high-doses (HD) with autologous hematopoietic stem cell transplantation (AHSCT). However, CSF and/or leptomeningeal relapse is frequent and effective therapeutic

strategies are lacking for these patients, whose survival remains low. Meningeal dissemination represents the rationale for using intrathecal (IT) therapy: overcoming the blood brain barrier, it allows for effective levels of chemotherapeutic agent to be achieved in CSF. Although well-established for the treatment of hematopoietic neoplasms involving the CNS, IT therapy is not usually included in protocols for meningeal metastatic tumors of the CNS.

The conventional agents used for IT administration have a short half-life in CSF, and this is limiting their cytotoxic effect (4). Liposomal cytarabine is a suspension of cytosine-arabinoside (Ara-C) encapsulated in multivesicular, lipid-based particles. At body temperature, the biodegradation of the lipid membranes leads to a gradual release of Ara-C ensuring prolonged cytotoxic concentrations in CSF. Liposomal cytarabine has been proven efficacious in lymphomatous and neoplastic meningeal involvement associated with solid tumors in adults, but it has only rarely been used for MB (5-8). We report our initial experience with IT liposomal cytarabine in three cases of relapsed MB.

Patients and Methods

Three children were treated with IT liposomal cytarabine; the IT therapy was administered every 15 days, at 2 mg/kg/dose (maximum dosage: 35 mg in children aged less than 13 years, 50 mg in older children) with concomitant dexamethasone (0.15 mg/kg/dose, twice day, orally for five days) to prevent arachnoiditis. The ethical committee approval for IT liposomal cytarabine was obtained for all patients. Informed written consent was obtained from the patients' parents or legal guardians.

All patients presented CSF and/or leptomeningeal MB. The IT treatment was associated with systemic chemotherapy namely cisplatin, lomustine and vincristine (every six weeks) for patient 1 and 3, and sorafenib for patient 2.

During treatment, a psychological support was proposed to all patients. Periodically, a pediatric Quality of Life (QoL) assessment was administered, at least every 2 months, in order to monitor the QoL (9).

Correspondence to: Angela Mastronuzzi, Division of Hematology/Oncology and Stem Cell Transplantation, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, 4-00165, Rome, Italy. Tel: +39 0668592129, Fax: +39 0668592292, e-mail angela.mastronuzzi@opbg.net

Key Words: Brain tumor, liposomal cytarabine, intrathecal, medulloblastoma, relapse/progression, case series.

Results

The IT therapy was well-tolerated in all patients, with only mild pain after the first administration, and without any toxicity related to IT treatment and procedure. All patients achieved a progression-free survival ranging from 4 to 11 months with a good QoL.

Patient 1 is a 6-year-old female diagnosed at 2 years and 9 months of age with localized, nodular desmoplastic MB, radically removed at surgery. She developed a first recurrence of disease in the dural sac 16 months after completion of first-line therapy and was treated with craniospinal radiation and second-line chemotherapy. Eight months after completion of second-line therapy, the child developed a second leptomeningeal recurrence with CSF dissemination. Salvage treatment with IT liposomal cytarabine associated with systemic chemotherapy was started. The IT therapy was well-tolerated, with only mild pain after the first administration and without toxicities being recorded. She maintained a good QoL with regular school attendance. CSF samples, analyzed before each drug administration, showed negativity for tumor cells from the first administration and a response at Magnetic Resonance Imaging (MRI) (Figure 1) performed after three months. The child was in good clinical condition for four months until a new progression occurred.

Patient 2 is a 17-year-old boy diagnosed at 14 years of age with M3 classical MB, with subtotal resection at surgery. Because of disease progression after first-line treatment, second- and third-line chemotherapies were administered and stable disease was maintained for 10 months. Considering the poor tolerance to the treatment and the persistence of diffuse leptomeningeal involvement, we shifted the patient to IT liposomal cytarabine. CSF samples were always negative for neoplastic cells. The treatment was well-tolerated, without transfusion requirement, and the boy was able to regularly attend school and practice daily living activities. MRI performed after the third administration showed stable disease. The patient manifested signs of progression after five months and further systemic chemotherapy was started. He is alive at 10 months with persistent disease.

Patient 3 is a 6-year-old female diagnosed at 4 years of age with M3 classical MB, partially removed surgically. Unfortunately, four months after the end of first-line therapy, she developed clinical and radiological recurrent disease, with diffuse leptomeningeal seeding and negative CSF. She was treated with second-line systemic chemotherapy alternating with IT liposomal cytarabine. The treatment was well-tolerated without any sign of arachnoiditis, but the child developed an important transfusion need, mainly for platelets, and neutropenic fever. While it is possible that liposomal cytarabine contributed to hematological toxicity, we believe it was mainly due to systemic chemotherapy. MRI performed after 5 months showed stable leptomeningeal involvement despite progression in parenchymal lesions.

Considering this response, the child underwent one further IT administration of the drug. She remains alive after 11 months with slow disease progression.

Discussion

Anticancer drugs most commonly used for IT administration include methotrexate, Ara-C, topotecan, etoposide and mafosfamide (10, 11). Pharmacokinetic studies have demonstrated that by this route of administration, while effective drug concentrations can be achieved in the CSF and in the leptomeninges, the brain tissue receives only a low concentration of drug (10). Therefore, this approach is an effective treatment for meningeal but not for parenchymal disease. Moreover, a few IT drugs can produce neurotoxic effects that limit their use (11-15).

Feasibility and safety of IT liposomal cytarabine administration to children with neoplastic meningitis was demonstrated by Bomgaars *et al.* in a phase I trial and reported also by Peyrl *et al.* in six children with CNS tumors (16, 17). However, subsequent studies, both in adult and pediatric patients, showed that this form of treatment was accompanied by severe adverse events, mainly neurological, when liposomal cytarabine was associated with systemic treatment (7, 18). These events were most frequently experienced in patients with leukemia who received IT methotrexate and radiotherapy, considering that these treatments cause *per se* a neurotoxicity.

Recently, few authors suggested a possible role of IT liposomal cytarabine in pediatric CNS tumors with a good tolerance (20-23).

In our series, we did not observe any relevant toxicity in children receiving concurrent intravenous chemotherapy, moreover, all children had previously received radiotherapy. Indeed, the treatment was well-tolerated, except for mild back pain reported by one child. No severe/life-threatening toxicities were recorded and no children needed to discontinue treatment. Concurrent use of dexamethasone successfully prevented arachnoiditis.

This small case series also suggests that liposomal cytarabine can be effective at controlling disease progression in children suffering from MB with leptomeningeal dissemination, even in multiply relapsed cases, as demonstrated by an arrest of leptomeningeal progression for 4 to 11 months. Concurrent systemic treatments possibly contributed to this result. Moreover, all children were able to achieve good QoL with an active psychological support, monitored periodically with a prospective assessment (9).

Many studies investigated strategies to overcome meningeal relapse and progression of MB, given its high propensity to disseminate in the CSF, while few studies focused on the efficacy of liposomal cytarabine in children suffering from MB. Promising results were shown in a recent study on 17 children with *de novo* or relapsed embryonal

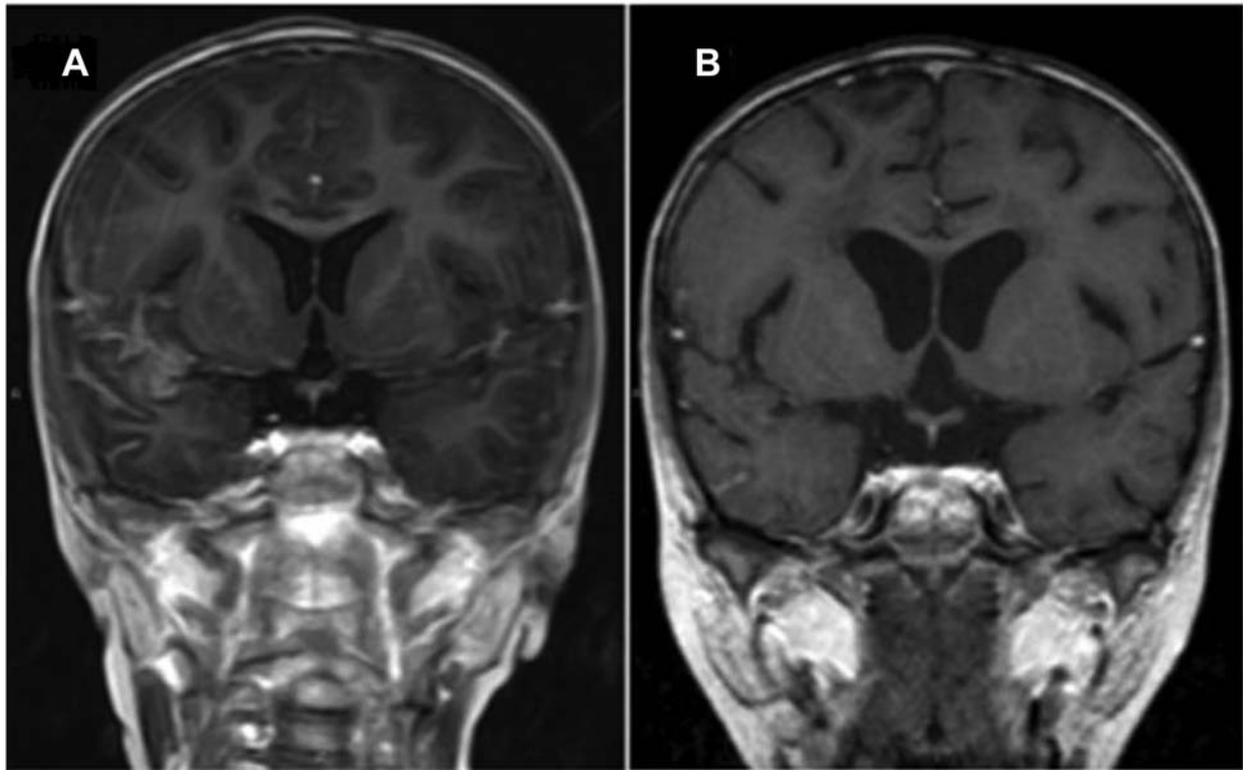


Figure 1. Patient 1, Magnetic Resonance Imaging (MRI) at relapse (A) and after 3 months of intrathecal therapy (B). The MRI shows an impressive reduction of leptomeningeal involvement.

tumors of the CNS, with objective responses and longer median time-to-progression and overall survival compared to other IT chemotherapeutics (8).

In conclusion, our experience suggests that the use of IT liposomal cytarabine associated with systemic drugs that can penetrate the brain tissue should be a valid strategy to control meningeal progression of MB, allowing at the same time a good QoL. Larger prospective phase II trials are needed to draw firm conclusions on long-term efficacy, toxic effects of IT liposomal cytarabine on the developing nervous system, and the best combination of systemic drugs.

Acknowledgements

We thank Professor Franco Locatelli for critically reading the manuscript.

References

- 1 Dhall G: Medulloblastoma. *J Child Neurol* 24: 1418-1430, 2009.
- 2 Ries LA, Smith MA, Gurney JG Linet M, Tamra T, Young JL and Bunin GR: Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. NIH Pub No 99-4649. Bethesda, MD: National Cancer Institute, SEER Program 51-63, 1999.
- 3 McNeil DE, Coté TR, Clegg L and Rorke LB: Incidence and trends in pediatric malignancies medulloblastoma/primitive neuroectodermal tumor: A SEER update. *Surveillance Epidemiology and End Results. Med Pediatr Oncol* 39: 190-194, 2002.
- 4 Zimm S, Collins JM, Miser J, Chatterji D and Poplack DG: Cytosine arabinoside cerebrospinal fluid kinetics. *Clin Pharmacol Ther* 35: 826-830, 1984.
- 5 Kripp M and Hofheinz RD: Treatment of lymphomatous and leukemic meningitis with liposomal encapsulated cytarabine. *Int J Nanomedicine* 3: 397-401, 2008.
- 6 Rueda Domínguez A, Olmos Hidalgo D and Viciano Garrido R: Liposomal cytarabine (DepoCyte) for the treatment of neoplastic meningitis. *Clin Transl Oncol* 7: 232-238, 2005.
- 7 Benesch M, Siegler N, Hoff Kv, Lassay L, Kropshofer G, Müller H, Sommer C, Rutkowski S, Fleischhack G and Urban C: Safety and toxicity of intrathecal liposomal cytarabine (Depocyte) in children and adolescents with recurrent or refractory brain tumors: A multi-institutional retrospective study. *Anticancer Drugs* 20: 794-799, 2009.
- 8 Partap S, Murphy PA, Vogel H, Barnes PD, Edwards MS and Fisher PG: Liposomal cytarabine for central nervous system embryonal tumors in children and young adults. *J Neurooncol* 103: 561-566, 2011.
- 9 Varni JW, Burwinkle TM, Katz ER, Meeske K and Dickinson P: The PedsQL in Pediatric Cancer: Reliability and Validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 94: 2090-2106, 2002

- 10 Fleischhack G, Jaehde U and Bode U: Pharmacokinetics following intraventricular administration of chemotherapy in patients with neoplastic meningitis. *Clin Pharmacokinet* 44: 1-31, 2005.
- 11 Slavic I, Schuller E, Falger J, Günes M, Pillwein K, Czech T, Dietrich W, Rössler K, Dieckmann K, Prayer D and Hainfellner J: Feasibility of long-term intraventricular therapy with mafosfamide (n=26) and etoposide (n=11): experience in 26 children with disseminated malignant brain tumors. *J Neurooncol* 64: 239-247, 2003.
- 12 Relling MV, Fairclough D, Ayers D, Crom WR, Rodman JH, Pui CH and Evans WE: Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *J Clin Oncol* 12: 1667-1672, 1994.
- 13 Blaney SM, Heideman R, Berg S, Adamson P, Gillespie A, Geyer JR, Packer R, Matthay K, Jaecckle K, Cole D, Kuttesch N, Poplack DG and Balis FM: Phase I clinical trial of intrathecal topotecan in patients with neoplastic meningitis. *J Clin Oncol* 21: 143-147, 2003.
- 14 Groves MD, Glantz MJ, Chamberlain MC, Baumgartner KE, Conrad CA, Hsu S, Wefel JS, Gilbert MR, Ictech S, Hunter KU, Forman AD, Pudukallu VK, Colman H, Hess KR and Yung WK: A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. *Neuro Oncol* 10: 208-215, 2008.
- 15 Savaraj N, Feun LG, Lu K, Gray K, Wang C and Loo TL: Pharmacology of intrathecal VP-16-213 in dogs. *J Neuro-Oncol* 13: 211-213, 1992.
- 16 Bomgaars L, Geyer JR, Franklin J, Dahl G, Park J, Winick NJ, Klenke R, Berg SL and Blaney SM: Phase I of intrathecal liposomal cytarabine in children with neoplastic meningitis. *J Clin Oncol* 22: 3916-3921, 2004.
- 17 Peyrl A, Saueremann R, Traunmueller F, Azizi AA, Gruber-Olipitz M, Gupper A and Slavic I: Pharmacokinetics and safety of intrathecal liposomal cytarabine in children aged <3 years. *Clin Pharmacokinet* 48: 265-271, 2009.
- 18 Jabbour E, O'Brien S, Kantarjian H, Garcia-Manero G, Ferrajoli A, Ravandi F, Cabanillas M and Thomas DA: Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. *Blood* 109: 3214-3218, 2007.
- 19 Benesch M, Sovinz P, Krammer B, Lackner H, Mann G, Schwinger W, Gadner H and Urban C: Feasibility and toxicity of intrathecal liposomal cytarabine in five children and young adults with refractory neoplastic meningitis. *J Pediatr Hematol Oncol* 29: 222-226, 2007.
- 20 Passarin MG, Moretto G, Musso AM, Ottaviani S, Masotto B, Ghimenton C, Iuzzolino P, Buffone E, Rudà R, Soffietti R, Vattemi E and Pedersini R: Intrathecal liposomal cytarabine in combination with temozolomide in low-grade oligoastrocytoma with leptomeningeal dissemination. *J Neurooncol* 97: 439-444, 2010.
- 21 Navajas A, Lassaletta A, Morales A, López-Ibor B, Sábado C, Moscardó C, Mateos E, Molina J, Sagasetta M and Sastre A: Efficacy and safety of liposomal cytarabine in children with primary CNS tumours with leptomeningeal involvement. *Clin Transl Oncol* 14: 280-286, 2012.
- 22 Chamberlain MC: Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyte) administered for the treatment of leptomeningeal metastases: A retrospective case series. *J Neurooncol* 109: 143-148, 2012.
- 23 Gaviani P, Corsini E, Salmaggi A, Lamperti E, Botturi A, Erbetta A, Milanesi I, Legnani F, Pollo B and Silvani A: Liposomal cytarabine in neoplastic meningitis from primary brain tumors: a single institutional experience. *Neurol Sci*, 2013 Mar 24. [Epub ahead of print].

Received May 14, 2013

Revised June 12, 2013

Accepted June 13, 2013