DS (Child) H J 2021; 37(1): 15-20

ORIGINAL ARTICLE

Neurological Complications of Intrathecal Chemotherapy in Children: Experience in A Tertiary Care Hospital in Bangladesh

Sheikh Farjana Sonia[1], Avijeet Kumar Mishra[2], Azmeri Sultana[3], Sharmin Afroze[4]

Abstract

Background: *Intrathecal (IT) chemotherapeutic agents have a narrow therapeutic index and high potential for toxicity. Though severe side effects are rare, but sometime consequences of IT chemotherapy can be catastrophic.*

Objectives: *The objective of the study was to observe the neurological complications of intrathecal chemotherapy administrations in patients getting treatment for childhood malignancy.*

Methods: *This prospective study included 33 patients who received IT chemotherapy on 76 occasions from July 2020 to December 2020 at Dr. M R Khan Shishu Hospital and ICH. We documented all the neurological complications within two weeks of IT chemotherapy. We defined minor neurological complications as headache, backache, fever, nausea, or vomiting. Major neurological complications were defined as nuchal rigidity, paresthesia, paralysis, or chemical arachnoiditis. All the cases were managed according to the internationally standard protocol.*

Results: *Among the patients who received IT chemotherapy 64% were male and 36% were female. The mean age of child was 7 years. The most common diagnosis was BCP (B cell precursor) ALL (75.8%), followed by T-cell ALL (15.1%), APML (Acute promyelocytic leukemia) (6.1%), and B lymphoblastic Lymphoma (3%). Therapy consisted of methotrexate alone in 73 (96.1%) occasions, and cytarabine alone in 3(3.9%) occasions. Minor events occurred in 17(22.4%) occasions but no patient developed major events after administration of IT chemotherapy. Among the side effects a total of 5 (6.6%) occasions children developed nausea, 4 (5.3%) had back pain, 3 (3.9%) had headache, 2 had (2.6%) vomiting, 2 (2.6%) had dizziness and 1(1.3%) developed fever after IT chemotherapy administration. No patient developed major neurological events like neck rigidity, paralysis and chemical arachnoiditis. About 77.6% occasions, children did not develop any side effects after IT chemotherapy administration.*

Conclusion: *No major toxic neurological events occurred but only minor neurological complications developed after IT chemotherapy administration. It is important for clinicians to be aware of the adverse events and consider them when treating patients with IT chemotherapy.*

Keywords: *Intrathecal chemotherapy, complications*

1. Assistant Professor, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH Dhaka, Bangladesh.
2. Clinical Fellow, Paediatric Haematology-Oncology and BMT, Great Ormond Street Hospital, London, United Kingdom.
3. Associate Professor, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH, Dhaka, Bangladesh.
4. Assistant Professor, Department of Neonatotology, Dr. M R Khan Shishu Hospital & ICH, Dhaka, Bangladesh.

Correspondence to: Dr. Sheikh Farjana Sonia, Assistant Professor, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH, Dhaka, Bangladesh. Cell: +8801752038848, E-mail: soniafarzana7@gmail.com

Received: 28 March 2021; **Accepted**: 27 May 2021

Introduction

Acute lymphoblastic leukemia and other aggressive lymphoid malignancies have high incidence of central nervous system (CNS) involvement. Various solid tumors, most notably neuroblastoma and nephroblastoma, can also metastasize in CNS as a late-stage complication causing devastating effects.[1]

Several treatment protocols have been developed targeting malignant cells in the CNS, among them the most commonly used modality of treatment is intrathecal (IT) chemotherapy. IT chemotherapy is frequently used for the prophylaxis and treatment of CNS metastasis.[1] It is introduced into the CSF after doing lumber puncture (LP). When drugs are given in this way, they are said to be given intrathecally.

The goal of IT chemotherapy is to the exposure of drugs to CNS, while reducing systemic drug toxicities.[2] The chemotherapeutic agents approved for intrathecal use include methotrexate, cytarabine, liposomal cytarabine, and thiotepa.[3,4] The scheduling and dosing of these medications varies depending on whether they are used for prophylaxis or treatment. Corticosteroids are frequently included with IT chemotherapy, most commonly hydrocortisone, to increase cytotoxicity and to decrease the risk of chemical arachnoiditis.[5] Most prophylactic regimens for leukemia and lymphomas contain methotrexate, either as a single agent or in combination with cytarabine.

The narrow therapeutic index and high potential toxicities of these agents can have potentially fatal consequences. Chemical arachnoiditis, an acute syndrome occurring hours after injection and characterized by headache, backache, vomiting, fever, meningismus and cerebral fluid pleocytosis is among the most common and potentially serious effects.[5,6] More severe symptoms also have been reported including cauda equina syndrome, encephalitis, papilledema, myelopathy, paraplegia, cranial nerve palsies, and seizures.[7,8]

Outcome of leukemia in children has shown a steady improvement, with recent trials demonstrating excellent survival in patients in the last few decades.[9,10] However, despite the advances in disease outcome, treatment related toxicity remains unacceptably high. Though severe side effects with IT chemotherapy are infrequent, outcome can sometimes be catastrophic. The true incidence of neurological complications is not well quantified. It is possible that the incidence of complications after IT chemotherapy in this setting is underestimated because cases may go unrecognized or unreported. The aim of this study was to describe the neurological side effects of IT chemotherapy administration.

Materials and Methods

This prospective study was conducted over a period of 6 months from July 2020 to December 2020 at Dr. M R Khan Shishu (Children) Hospital & Institute of Child Health, a tertiary care hospital of Dhaka city after approval from Ethical Review Committee. All children (Age: 1-18 years) getting intrathecal chemotherapy seeking treatment at our center were included. A total of 76 intrathecal chemotherapy were administered during this study period. An informed written consent was taken from parents and assurance about confidentiality was given.

The procedure of lumber puncture (LP) was explained in simple wards to patients and parents. The Paediatric Haemato-Oncology consultant did the procedure and one experienced nurse assisted the procedure. LP was performed under strict aseptic precaution with 25G spinal needles inserted in the L2-L3 or L3-L4 interspace. Patients were placed in their lateral decubitus position with knees flexed; and intrathecal chemotherapy was administered afterwards. Patient diagnosed as ALL and Lymphoma received methotrexate and patient diagnosed as APML received cytarabine as intrathecal medication. Sedation was not used in any case. Patients were asked to drink adequate liquids and they were asked to take rest in bed for the subsequent 3-4 hours on a routine basis. Patients were also advised not to use pillow to sleep for the subsequent 24 hours.

Table I

Dose of Intrathecal Methotrexate according to age

Age	Dose of Methotrexate (Intrathecal)
<2year	8 mg
2-3 year	10 mg
>3 year	12 mg

We documented signs and symptoms of neurotoxicity that were not present before administration but developed acutely thereafter. Development of new symptoms indicative of neurotoxicity and/or arachnoiditis within fourteen days of administration of IT chemotherapy, specifically paralysis, paresthesia, headache, back pain, nuchal rigidity,

fever, nausea, or vomiting were recorded. We documented only new-onset symptoms because the systemic changes like fever, nausea, vomiting, and asthenia, which may be associated with chemical arachnoiditis may also occur for other reasons in this patient population. We defined minor neurological complications as headache, backache, fever, nausea, or vomiting. Major neurological complications were defined as nuchal rigidity, paresthesia, cranial nerve palsy, paralysis, or chemical arachnoiditis. This division was to allow distinction between more serious neurologic toxicities associated with IT chemotherapy from events with less impact on quality of life.

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and as numbers (%) for categorical data. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-20).

Results

During the study period, 76 intrathecal chemotherapy administrations were performed in 33 patients, of whom 21 (64%) were male and 12 (36%) were female. The mean age of child was 7 years (range 2 to 15 years). The most common diagnosis was BCP (B cell precursor) ALL (75.8%), followed by T-cell ALL (15.1%), APML (Acute promyelocytic leukemia) (6.1%), and B Lymphoblastic Lymphoma (3%) which is shown in table II. Therapy consisted of methotrexate alone in 73 (96.1%) occasions, and cytarabine alone in 3 (3.9%) occasions.

Table II
Demographic characteristics of patients received IT chemotherapy (N=33)

Characteristics	Parameter
Age in years (mean ±SD)	7.7 ±7
Sex (%)	
Male	64
Female	36
Diagnosis (%)	
BCP ALL	75.8
T ALL	15.1
APML	6.1
B lymphoblastic lymphoma	3
Type of Chemotherapy (%)	
Methotrexate received	96.1
Cytarabine received	3.9

The symptoms developed after administration of IT chemotherapy are shown in Figure 1. No patient developed major adverse events like neck rigidity, paresthesia, paralysis and chemical arachnoiditis. Among the side effects a total of 5 (6.6%) occasions, children developed nausea, 4 (5.3%) occasions had back pain, 3 (3.9%) had headache, 2 had (2.6%) vomiting, 2 (2.6%) had dizziness and 1 (1.3%) developed fever after IT chemotherapy administration. About 77.6% occasions, children did not develop any side effects after IT chemotherapy administration.

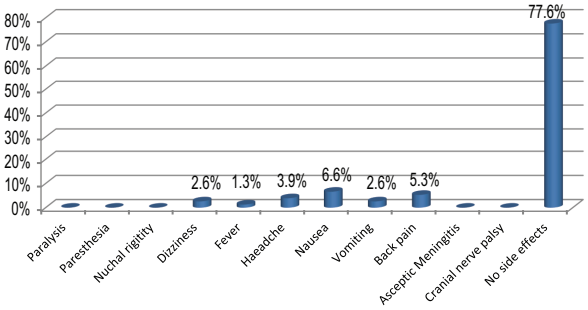

Fig.-1 *Side effects that developed after IT chemotherapy administration*

Minor events occurred in 17 occasions (22.4%) after IT chemotherapy administration. Among the minor side effects maximum child had nausea 29.4% followed by back pain 23.5%, headache 17.6%, vomiting 11.8%, dizziness 11.8%, and fever 5.9% (Figure2). All the cases were managed conservatively on OPD basis according to unit protocol. No patient required admission for these minor events.

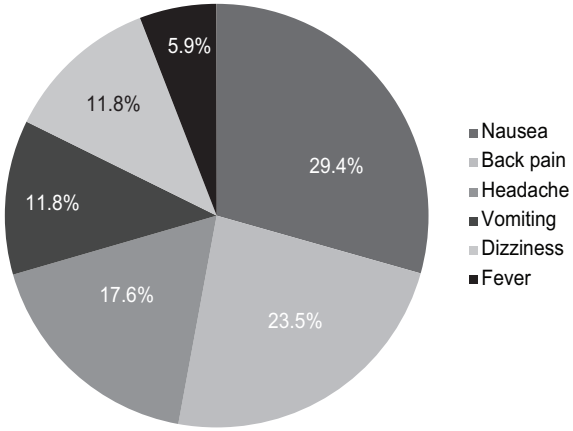

Fig.-2 *Minor side effects that developed after IT chemotherapy*

Discussion

IT chemotherapy for both therapy and prophylaxis of CNS involvement has been a mainstay for medical management of leukemia and lymphoma throughout the world for several decades and for patients with leptomeningeal involvement by solid tumors.[6] We report the adverse neurologic events following IT chemotherapy used as prophylaxis for CNS involvement at our center over six months period. No child developed major neurotoxicity after IT chemotherapy administration. We found minor side effects in 17 cases (22.4%) after administration of IT chemotherapy.

Survival for patients with leptomeningeal spread of disease is low while the incidence of early and late complications associated with IT chemotherapy is high.[11-13] Several studies showed the overall incidence of acute neurotoxicity from IT MTX in children is 3-11%.[14] The incidence of minor side effects after IT chemotherapy is 26-30%.[1] In our study we found minor side effects after IT chemotherapy in 22.4% cases.

Although symptoms such as headache and back pain related to lumbar puncture are not uncommon, clinicians should also be cognizant that these symptoms may signify impending onset of more significant toxicity. Methotrexate is typically assumed to be the major cause of such neurotoxicities,[14] but cytarabine is also a known major cause.[15-17] Jabbour et al[7] evaluated neurologic complications secondary to IT liposomal cytarabine in combination with high-dose methotrexate as prophylactic treatment in patients with ALL and found the incidence of severe complications to be 16%.

Geiser et al[18] found that a toxic syndrome characterized by fever, headache, and vomiting, lasting 2-5 days, occurred in 61% of 39 children with acute leukemia in complete remission, receiving central nervous system prophylaxis with intrathecal methotrexate, and in 14% of 34 children receiving the same plus cranial radiation. The syndrome was accompanied by pleocytosis with lymphocytes, monocytes, and neutrophils. Our study did not find any serious toxic effects.

In a study done by Byrnes et al[19] found that the incidence of major neurologic adverse event was 6.8% and the rate of minor neurologic event was 38.3% for all cases of patients receiving IT chemotherapy. The adverse events encountered most frequently were headache (15.9%), nausea (13.6%), vomiting (9.6%), back pain (5.8%), and fever (5.8%). The most frequent major adverse events were asthenia (4.3%) and paresthesia (3.8%). In our study the rate of minor neurologic event was 22.4%, among them the most frequent adverse effect was nausea (6.6%) followed by back pain (5.3%), headache (3.9%), vomiting (2.6%), dizziness (2.6%) and fever (1.3%).

In the case of IT chemotherapy, there is chance of contamination of the IT methotrexate. Zeng et al[20] investigated the development of paraplegia amongst the patients who received IT methotrexate, discovering trace amounts of vincristine that contaminated intrathecal drugs produced by a manufacturing plant in China causing a large outbreak of severe neurological damage. Murata et al[21] reported a case of demyelination secondary to myelopathy attributed to an IT methotrexate dose. When there is outbreak of severe adverse reactions due to IT chemotherapy, especially when temporally related, one should suspect potential chemotherapy contamination.

Olmos-Jimenez et al[22] performed an observational and prospective study in Spain evaluating standardized triple intrathecal chemotherapy in hematology-oncology patients over an 18-months period. Adverse events occurred in 39.3% of 56 doses. The adverse event recorded most frequently was headache, followed by vomiting and vertigo. In one occasion (1.8%) there was grade 2 sensorimotor polyneuropathy. But in our study the most frequent adverse event recorded was nausea and we did not find any child with neuropathy.

Riva et al[23] found that the most common adverse effect after intrathecal chemotherapy was headache (50%). Other complications observed were lumbar pain in seven patients and transient paresthesia in the legs of one patient. Severe complications were not observed in this study which is similar to our study.

The minor adverse events that developed after IT chemotherapy administration could be due to concomitant administration of other systemic chemotherapy which we did not investigate. Future studies should be done to demonstrate whether concurrent administration of other systemic chemotherapeutic agents may cause the adverse neurological events.

Conclusion

Our study shows that IT chemotherapy related complications are frequently mild. No major toxic events occurred after IT chemotherapy administration in our study. Oncologist should be aware of the potential complications and uncontaminated chemo-therapeutic agents as well as strict aseptic precaution should be taken to prevent the serious adverse neurological complications.

References

1. Byrnes DM, Vargas F, Dermarkarian C, Kahn R, Kwon D, Hurley J, et al. Complications of intrathecal chemotherapy in adults: Single-institution experience in 109 consecutive patients. *Journal of oncology* 2019. Doi: 10.1155/2019/4047617.
2. Kerr JZ, Berg S, Blaney SM. Intrathecal chemotherapy. *Critical reviews in oncology/hematology* 2001;**37**:227-36.
3. Kak M, Nanda R, Ramsdale EE, Lukas RV. Treatment of leptomeningeal carcinomatosis: current challenges and future opportunities. *Journal of Clinical Neuroscience* 2015;**22**:632-37.
4. Mack F, Baumert BG, Schäfer N, Hattingen E, Scheffler B, Herrlinger U, et al. Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treatment Reviews* 2016;**43**:83-91.
5. Kwong YL, Yeung DY, Chan JC. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. *Annals of hematology* 2009;**88**:193-201.
6. Bleyer WA. The clinical pharmacology of methotrexate. New applications of an old drug. *Cancer* 1978;**41**:36-51.
7. Jabbour E, O'Brien S, Kantarjian H, Garcia-Manero G, Ferrajoli A, Ravandi F, et al. Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. *Blood* 2007;**109**:3214-18.
8. Bhojwani D, Sabin ND, Pei D, Yang JJ, Khan RB, Panetta JC, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *Journal of clinical oncology* 2014;**32**:949.
9. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE, Raimondi SC, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;**24**:371-82.
10. Hunger SP, Lu X, Devidas M. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol* 2012;**30**:1663-69.
11. Grant R, Naylor B, Greenberg HS, Junck L. Clinical outcome in aggressively treated meningeal carcinomatosis. *Archives of Neurology* 1994;**51**:457-61.
12. Glantz MJ, Cole BF, Recht L, Akerley W, Mills P, Saris S, et al. High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: is intrathecal chemotherapy necessary? *Journal of Clinical Oncology* 1998;**16**:1561-67.
13. Fizazi K, Asselain B, Vincent Salomon A, Jouve M, Dieras V, Palangie T, et al. Meningeal carcinomatosis in patients with breast carcinoma: Clinical features, prognostic factors, and results of a high dose intrathecal methotrexate regimen. Cancer: Interdisciplinary *International Journal of the American Cancer Society* 1996;**77**:1315-23.
14. Shuper A, Stark B, Kornreich L, Cohen IJ, Aviner S, Steinmetz A, et al. Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *Journal of Child Neurology* 2000;**15**:573-80.
15. Pérez-Larraya JG, Palma JA, Carmona-Iragui M, Fernández-Torrón R, Irimia P, Rodríguez-Otero P, et al. Neurologic complications of intrathecal liposomal cytarabine administered prophylactically to patients with non-Hodgkin lymphoma. *Journal of Neuro-Oncology* 2011;**103**:603-09.
16. Ostermann K, Pels H, Kowoll A, Kuhnhenn J, Schlegel U. Neurologic complications after intrathecal liposomal cytarabine in combination with systemic polychemotherapy in primary CNS lymphoma. *Journal of Neuro-oncology* 2011;**103**:635-40.
17. Levinsen M, Harila-Saari A, Grell K, Jonsson OG, Taskinen M, Abrahamsson J, et al. Efficacy and toxicity of intrathecal liposomal cytarabine in first-line therapy of childhood acute lymphoblastic leukemia. *Journal of pediatric hematology/oncology* 2016;**38**:602-09.
18. Geiser CF, Bishop Y, Jaffe N, Furman L, Traggis D, Frei E. Adverse effects of intrathecal methotrexate in children with acute leukemia in remission. *Blood* 1975;**45**:189-95.

19. Byrnes DM, Dermarkarian CR, Kahn R, Kwon D, Vargas F, Hurley J, et al. Incidence of neurological complications secondary to intrathecal chemotherapy used as either prophylaxis or treatment of leptomeningeal carcinomatosis. *Blood* 2016;**128**:5973.

20. Zeng G, Ma H, Wang X, Yan H, Wan X, Jiang B, et al. Paraplegia and paraparesis from intrathecal methotrexate and cytarabine contaminated with trace amounts of vincristine in China during 2007. *Journal of Clinical Oncology* 2011;**29**:1765-70.

21. Murata KY, Maeba A, Yamanegi M, Nakanishi I, Ito H. Methotrexate myelopathy after intrathecal chemotherapy: a case report. *Journal of Medical Case Reports* 2015;**9**:1-4.

22. Olmos-Jiménez R, Díaz-Carrasco MS, Cabañas-Perianes V, Pulido MV, Espuny-Miró A. Evaluation of standardized triple intrathecal therapy toxicity in oncohematological adult patients. *Farmacia Hospitalaria* 2017;**41**:611-17.

23. De la Riva P, Andres-Marín N, Gonzalo-Yubero N, Tainta-Cuezva M, Caminos N, Urtasun-Ocariz MÁ, et al. Headache and other complications following intrathecal chemotherapy administration. *Cephalalgia* 2017;**37**:1109-10.