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# Intra-Cerebrospinal Fluid Chemotherapy is New direction in Pediatric Solid Tumors with Leptomeningeal Metastasis

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## Abstract

**Introduction:** Intra-Cerebrospinal Fluid (CSF) chemotherapy defines as chemotherapy drugs administration in the brain/spine fluid compartment which can be used for leptomeningeal metastases in infiltrative tumors consisting of leukemia and lymphoma.

**Material and Methods:** We search via the internet, using the online medical database "Pubmed" and the more generic search-engine "Google Scholar".

**Results:** Collection, spanning over 20 years, was searched, as were recent issues of journals in which articles on the subject are most often found, were original articles.

**Conclusion:** We introduce several intra-CSF chemotherapy regimens in solid tumors.

**Keywords: Intrathecal chemotherapy; Leptomeningeal metastasis; Pediatric; Brain tumor**

## Introduction

Intra-Cerebrospinal Fluid (CSF) chemotherapy define as chemotherapy drugs administration in the brain/spine fluid compartment which can be used for leptomeningeal metastases in infiltrative tumors consisting of leukemia and lymphoma since some years ago, but intra-CSF chemotherapy drugs administration by way of this procedure for stable tumors remedy isn't glaringly. That is a brand new insight and approach for fighting towards leptomeningeal metastasis of solid tumors. This technique is completed with 2 methods: 1) intratechally 2) intraventricular through Ommaya reservoir. Co-administration of this technique with conventional chemotherapy in metastatic embryonic tumors among younger kids has arguable outcomes. In this technique is tried to supply excessive doses of chemotherapy to the coating regions of the brain to lessen ailment relapse in those regions [1-3].

Intrathecal chemotherapy treats subclinical leptomeningeal deposits and tumor cells floating in the cerebrospinal fluid, preventing in addition seeding [4].

The prevalence of aggregate intrathecal healing procedures over single marketers' intrathecal therapies is controversy. Some trials have shown no distinction among single-agent Methotrexate and combined remedy. Combination remedies may be greater neurotoxic than single agents [5].

Use of intraventricular Ommaya reservoir has the gain of affected person compared to the intrathecal chemotherapy.

Although this modality of treatment provides high attention of the drug on the web site of the tumor. Also it lamentably exposes the normal brain to these higher concentrations with a potential to cause more adverse effects [6,7].

Thiotepa and Methotrexate (MTX) is the one of the old chemotherapy drugs has administered intra-CSF. Thiotepa is cleared from CSF within a few minutes and has survival curves similar to those of MTX with less neurologic toxicity than MTX. In spite of leukoencephalopathy secondary to intraventricular excessive dose of methotrexate, low-dose methotrexate can be infused into the fourth ventricle in patients with recurrent, malignant tumors without inflicting diagnosed neurological deficits or different widespread toxicity.

Recently, new agents introduced for intra-CSF chemotherapy. A few studies define intra-CSF chemotherapy does no longer extend patient survival and considerably increases associated

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**Table 1**: Maximum 2 intrathecal chemotherapy remedies weekly (eg. Monday and Thursday) give one drug each remedy.

| **TREATMENT**: | | |
|---|---|---|
| **Drug** | **Dose** | **BCCA Administration Guideline**<br>• **by physician only**<br>• **lumbar puncture tray required if no Ommaya reservoir** |
| Methotrexate | 12 mg once or twice weekly* | Intrathecal (via lumbar puncture or Ommaya ventricular reservoir) qs to 6 mL **preservative-free** NS |
| *or | | |
| Thiotepa | 12 mg once or twice weekly* | Intrathecal (via lumbar puncture or Ommaya ventricular reservoir) qs to 6mL **preservative-free** NS |
| *or | | |
| Cytarabine | 50 mg once or twice weekly* | Intrathecal (via lumbar puncture or Ommaya ventricular reservoir) qs to 6 mL **preservative-free** NS |

neurotoxicities [8].

## Material and Methods

The literature search was carried out via the internet, using the online medical database "Pubmed" supported by the US National Library of Medicine and the more generic search-engine "Google Scholar".

A narrative literature search was undertaken and maintained up to date during the review. The MEDLINE and Pubmed electronic reference database was searched using keywords and phrases base on expert opinions and similar publications include: leptomeningeal metastasis solid tumor, intrathechal chemotherapy, intra-CSF chemotherapy. Collection, spanning over 20 years, was searched, as were recent issues of journals in which articles on the subject are most often found.

## Results

A total of 31 publications (21 include and 67 exclude) during 1995-2017, met eligibility criteria for this review was base on successful experiences for intra-CSF chemotherapy on solid tumors.

We found some chemotherapy drugs for intra-CSF chemotherapy for solid tumors treatment in the literature and suggest two standard intrathechal chemotherapy regimens for pediatric solid tumors.

## Discussion

Some intra-CSF chemotherapy regimens in solid tumors were suggested for intra-CSF chemotherapy in adult and pediatric during two decades.

Traditionally, intra-CSF drug remedy is constrained to 3 chemotherapeutic drugs (Methotrexate, Cytosine arabinoside and Thiotepa) administered through intralumbar or intraventricular drug delivery schedules [9].

Cytarabine isn't powerful for solid tumors but is beneficial in leukemic and lymphomatous meningitis. It's far now available in liposome-encapsulated shape (depoCyt) that can be administered each 2 weeks rather than 2-three times every week and consequences in an extended time to sickness progression and higher quality of life than treatment with MTX [10].

Thiotepa can be use as the second line agent after MTX and Cytarabine [11].

Intraventricular Methotrexate is used for non disseminated tumors that were absolutely resected. Five-year free survival after the addition of Methotrexate is envisioned approximately 60%. Just 3% to 5% of systemically administered MTX penetrates the Blood-Brain Barrier (BBB) at a half of clearance time of 6 h. Single intraventricular injection of MTX (6.25 mg/m$^2$) can achieve healing awareness inside the lumbar area for 48 h at a minimal systemic absorption (<0.1 μM) [12].

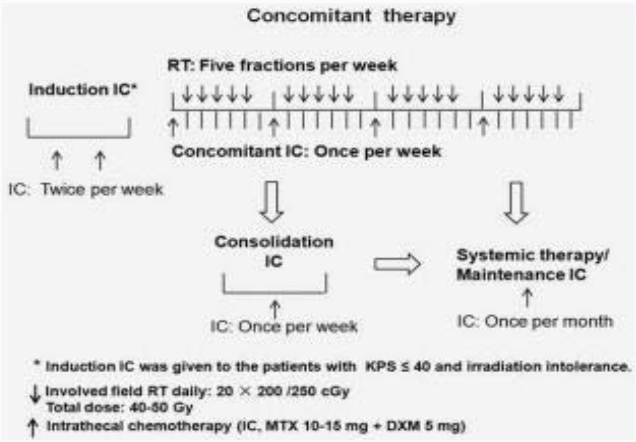


**Figure 1:** Protocol schema.
IC or ITC: Intrathecal Chemotherapy; RT: Radiation Therapy; KPS: Karnofsky Performance Score; MTX: Methotrexate; DXM: Dexamethasone

In brain tumors intraventricular Methotrexate remedy changed into extra suited and possible and usually properly tolerated. In this technique infections were the maximum common complication. A higher cumulative dose of intraventricular Methotrexate changed into related to better survival [12].

In meningeal carcinomatosis with concomitant parenchymal brain metastasis, management of repeated courses of Intrathecal Chemotherapy (ITC) consistent with the following alternated weekly time table is suggested: day 1: Thiotepa 10 mg, Methotrexate 15 mg, Hydrocortisone 30 mg; day five: Cytarabine (Ara-C) 70 mg, Methotrexate 15 mg, Hydrocortisone 30 mg, folinic acid 15 mg became given orally, every six hours after Methotrexate on days 2-3 and 6-7 confirm the controversial role of ITC [13].

The Position of intrathecal/intraventricular chemotherapy in number one CNS lymphoma (PCNSL) isn't described. MTX, Ara-C and corticosteroids were given via lumbar or ventricular (through a subgaleal reservoir) routes as a part of systemic chemotherapy regimens: MTX 12 mg two times per week became given by using lumbar path in trials, but intraventricular packages offer decrease day by day doses to attain sustained CSF tiers [14].

Some chemotherapy or biologic agents for leptomeningeal carcinomatosis include:

Mafosfamide is a shape of Cyclophosphamide that is energetic intrathecally and has little neurotoxicity aside from complications.

Mafosfamide at a dose of 20 mg a few times weekly is run until remission is achieved, follow by weekly administrations as consolidation therapy, and every 3 to 4 weeks thereafter for maintenance therapy [15].

Rituximab has been given intrathecally and is likewise prescribed (from lymphoma handiest). Dose of Rituximab ranged from 10 mg to 40 mg. An initial dose of 10 mg became used most usually and step by step escalated to clinical response or affected person tolerance. Rituximab doses encompass: 10 mg, 25 mg or 50 mg were administered diluted in normal saline (NaCl 0.9%) or undiluted as immediately drug throughout a period of 1 min to 5 min [16].

Trastuzumab has been given intrathecally to deal with Leptomeningeal Cancer (LC) from breast cancers. First ventricular injection of 50 mg of trastuzumab changed into administered (cycle 1) and, after a 21-day interval, trastuzumab became injected at a dose of 50 mg inside the ventricle and at a dose of 6 mg/kg intravenously (cycle 2; intravenous). The timing and the doses of later ventricular injections were set up in keeping with the pharmacokinetic profile of trastuzumab concentrations inside the CSF. On days 1, 2, 4, 7, and 14 of those first cycles, trastuzumab concentrations had been measured with the aid of Enzyme-Linked Immunosorbent Assay (ELISA) in lumbar and ventricular CSF, and in peripheral blood [17].

There are case reports of LC from Non-Small Cellular Lung Cancers (NSCLC) or breast cancer responding to intrathecal gemcitabine, trastuzumab, letrozole, and tamoxifen [18].

Immunotoxins, which includes monoclonal antibodies coupled with a protein toxin or radioisotope, appear powerful and are being studied. Compartmental intrathecal antibody-based Radioimmunotherapy (cRIT) administration in recurrent metastatic Central Nervous System (CNS) neuroblastoma following surgical operation is one of the theses alternatives.

cRIT-containing salvage regimen incorporating intrathecal I-131 Monoclonal Antibodies (MoAbs) targeting GD2 or B7H3 following surgical procedure and radiation or, 1 or 2 monthly injections $^{131}$I-8H9 (10-60 mci/injection) [19].

Furthermore, unwell-described delayed neurotoxicity turned into not able to be differentiated from disorder progression.

We introduce general protocol for intrathecal chemotherapy includes Dexamethasone and MTX treating leptomeningeal metastasis from solid tumors with adverse prognostic factors.

The regimen consisted of ITC through lumbar punctures:

1. Induction ITC (MTX 12.5 mg to 15 mg, plus Dexamethasone 5 mg, two times according to week).

Then these sufferers were allowed to acquire concomitant therapy upon neurologic improvement and radiotherapy tolerance. Supporting therapy became given to patients with low kps score.

2. Concomitant therapy includes consolidation ITC and fractional RT (MTX 12.5 mg to 15 mg, plus Dexamethasone 5 mg, as soon as in keeping with week, 4 weeks in total) and IF-RT.

Radiotherapy consisted of fractionated, conformal radiation given at a daily dose of 2 Gy. The making plans volume consisted of sites of symptomatic ailment, bulky disease found on MRI, such as the entire brain and basis cranii received 40 Gy in 20 fractions and/or segment of spinal canal acquired 40 Gy to 50 Gy (the above segments of the first lumbar vertebra had been given 40 Gy in 20 fractions; the primary lumbar vertebra and the inferior segments were given 40/50 Gy in 20 fractions) (Figure 1).

Patients with KPS ≤ 40 and irradiation intolerance were required to get hold.

Next treatment changed into advocated after concomitant remedy.

- Consolidation ITC: (MTX 12.5 mg to 15 mg, plus Dexamethasone 5 mg) become endorsed as soon as consistent with week.

The full cycles of ITC which include the induction therapy, concomitant therapy and consolidation therapy ought to be <8 times within 2 months.

Three protections ITC (MTX 12.5 mg to 15 mg, plus Dexamethasone 5 mg) become encouraged once a month. After concomitant therapy and/or consolidation therapy to patients with strong systemic sickness or longer expected survival. The patients with energetic systemic ailment had been proposed to systemic therapy (chemotherapy or molecular goal therapy) consistent with the NCCN suggestions of associated tumors [20].

BCCA protocol precis for strong tumors the usage of intrathecal methotrexate and/or Thiotepa and/or Cytarabine:

Drugs may be alternated (e.g. methotrexate alternating with Thiotepa for a maximum of 2 intrathecal chemotherapy injection in week) or single sellers can be used (Table 1). Methotrexate and Thiotepa are most commonly utilized in breast cancers and cytarabine in lymphomas but, the oncologist may use any of the above depending on the scientific scenario. The ITC are generally given two times a week for 2-4 weeks and then once weekly for a complete of 10-12 treatments if there may be a reaction (advanced signs and symptoms and reduced malignant cells in CSF). If there may be no response, radiation or supportive care simplest are options for treatment.

In summary, primary or metastatic brain involvements can be treated with intra-CSF chemotherapy in combination with other treatment modalities. This procedure has a greater importance in pediatric oncology and younger age kids with radiation therapy limitation.

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