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# Practical aspects of the use of intrathecal chemotherapy

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REVISIONES

# Practical aspects of the use of intrathecal chemotherapy

## Aspectos prácticos de la utilización de quimioterapia intratecal

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**Abstract**

**Introduction:** Intrathecal chemotherapy is frequently used in clinical practice for treatment and prevention of neoplastic meningitis. Despite its widespread use, there is little information about practical aspects such as the volume of drug to be administered or its preparation and administration.

**Objective:** To conduct a literature review about practical aspects of the use of intrathecal chemotherapy.

**Materials:** Search in PubMed/ Medline using the terms "chemotherapy AND intrathecal", analysis of secondary and tertiary information sources.

**Results:** The most widely used drugs in intrathecal therapy are methotrexate and cytarabine, at variable doses. One of the aspects with higher variability among different studies is their potential combination with a glucocorticoid, the specific corticoid selected and its dose. The efficacy and toxicity of the different combinations have not been compared. Regarding preparation, it is worth highlighting the recommendation to adjust pH and osmolarity to the physiological range, with the aim of improving tolerability. The volume of administration can influence distribution, and recommendated range is between 5 and 12 mL. Overall, it is recommended to extract a similar volume of cerebrospinal fluid before administration. The position of the patient during and after administration can have an impact on distribution and toxicity; lateral decubitus or sitting position is recommended in the first case, and prone and/ or supine position in the second one. Most publications don't explain how the treatment has been prepared or administered, and the lack of standardization could affect results.

**Conclusions:** There is a great variability in practice when using intrathecal chemotherapy, despite being an effective therapy, accepted by all international groups. This uncertainty is not li mited to the drugs and doses administered, but it also includes the manner of preparation and the administration technique. The heterogeneity in clinical practice can influence the efficacy and toxicity of this therapy.

**KEYWORDS:** Chemotherapy++ Intrathecal++ Administration++ Preparation++ Dosing.

**Resumen**

**Introducción:** La quimioterapia intratecal es utilizada frecuentemente, en la práctica clínica, para el tratamiento y prevención de la meningitis neoplásica. A pesar de su uso extendido, existe poca información acerca de aspectos prácticos tales como el volumen de fármaco a administrar o la forma de preparación y administración.

**Objetivo:** Realizar una revisión de la literatura acerca de aspectos prácticos de la utilización de la quimioterapia intratecal. *Material:* Búsqueda en PubMed/Medline utilizando los términos "chemotherapy AND intrathecal", análisis de fuentes de información secundarias y terciarias.
**Resultados:** Los fármacos más utilizados en terapia intratecal son metotrexato y citarabina, con dosis variables. La asociación o no con un glucocorticoide, el corticoide concreto seleccionado y su dosis es uno de los aspectos con mayor variabilidad entre distintos estudios. No se han comparado la eficacia y toxicidad de las distintas combinaciones. En la preparación destaca la recomendación de ajustar pH y osmolaridad al rango fisiológico, con el objetivo de mejorar la tolerancia. El volumen de administración puede influir en la distribución, oscilando las recomendaciones entre 5-12 mL. En general, se aconseja extraer previamente un volumen de líquido cefalorraquídeo similar. La posición del paciente durante y tras la administración puede influir en la distribución y la toxicidad; se recomienda el decúbito lateral o la sedestación, en el primer caso, y el decúbito prono y/o supino, en el segundo. La mayoría de las publicaciones no indican cómo se ha preparado o administrado el tratamiento, y la falta de estandarización podría afectar a los resultados.
**Conclusiones:** Existe gran variabilidad en la práctica a la hora de utilizar la quimioterapia intratecal, a pesar de ser una terapia efectiva asumida por todos los grupos internacionales. La incertidumbre no se limita a los fármacos y dosis administradas, sino que se extiende a la forma de preparación de las mezclas y la técnica de administración. La heterogeneidad en la práctica clínica puede influir en la efectividad y toxicidad de esta terapia.
**PALABRAS CLAVE:** Quimioterapia, Intratecal, Administración, Preparación, Dosificación.

## Introduction

The administration of intrathecal (IT) chemotherapy for the treatment and prevention of neoplastic infiltration in the central nervous system (CNS) is a widely extended practice that has demonstrated efficacy in different conditions. The use of such therapy for the prevention of CNS relapse in Acute Lymphoblastic Leukemia (ALL) in paediatric patients started in the 70s. The disease prognosis changed radically, because before the use of CNS prophylaxis, more than half of complete remissions induced by systemic chemotherapy would end up in CNS relapse[1]. IT chemotherapy has progressively displaced radiotherapy in this indication, given its similar efficacy with a more favourable profile of adverse effects[2]. Traditionally, the drugs used have been methotrexate and cytarabine, alone or in combination with glucocorticoids, in the called Triple Intrathecal Therapy (TIT). The use of liposomal cytarabine has been recently introduced, as well as monoclonal antibodies such as rituximab and trastuzumab for different indications. However, even though the use of IT chemotherapy is widely accepted by the scientific community, there is a great variability in practice, in aspects such as the specific drugs and doses used, the way of preparation (volume, type of disolvent, etc.), and the administration technique. The objective of this article is to review the information available about these practical aspects.

## Methods

A search was conducted in Pubmed/Medline, using the free terms "chemotherapy AND intrathecal". The most clinically relevant articles were selected for this review, based on the development or description of relevant practical aspects regarding the preparation and administration technique of the IT treatment. The search was complemented with the review of quotes included in the selected articles, and the analysis of secondary information sources.

## Results

### *Technique for intrathecal administration of drugs*

Intrathecal administration consists in the direct injection of the drug into the CNS[3]. This way of administration is occasionally necessary in order to achieve therapeutic concentrations in the CNS, which is protected by the blood-brain barrier (BBB). The blood-brain barrier is a complex structure formed by endothelial cells from the CNS capillary network, which prevents the free exchange of ions and organic molecules between the blood plasma and the nervous system[4], thus protecting the CNS from potentially neurotoxic agents; but this also makes it difficult for some drugs to reach therapeutic concentrations.

Cerebrospinal fluid (CSF) regulates the chemical environment of the CNS. The total volume of CSF in adults is 125-150 ml, with a formation and reabsorption rate of approximately 20 mL/hour; therefore it is completely renewed 3 times per day. CSF secretion and reabsorption is balanced in the majority of healthy adults, in order to keep an intracranial pressure below 150 mm$H_20$; an increase in intracranial pressure can entail severe complications. Normal CSF is clear, transparent and colourless. Its main physicochemical properties appear in Table 1.

**Table 1**
*Physicochemical properties of CSF*

| Parameter | Normal cerebrospinal fluid |
|---|---|
| Aspect | Crystalline |
| Cells | 0 – 5 / mm³ (lymphocytes) |
| Proteins | 15 – 45 mg /dL |
| Glucose | 50 – 80 mg/dL |
| Chlorides | 116 – 122 mEq/L |
| Sodium | 117 – 137 mEq/L |
| Potassium | 2.3 – 4.6 mEq/L |
| Osmolarity | 292 – 297 mOsm/L |
| Density | 1.0005 – 10007 g/mL |
| pH | 7.31 |

CSF volume varies with age. The CSF volume in newborns is approximately 40-60 ml, and it undergoes a fast increase during the first years of life, so that the CSF volume in ≥3-year-old children is equivalent to that of adults.

Drug administration in the CNS can be conducted through two methods: into the lumbar thecal sac by lumbar puncture (LP), or directly into the lateral ventricle through a subcutaneous reservoir and ventricular catheter (*Ommaya* Reservoir)[3].

*Lumbar Puncture*

Lumbar Puncture is an invasive technique for accessing the subarachnoid space, with diagnostic and therapeutic aims. The position of the patient is important for this procedure: they can be in lateral decubitus, which is the preferred position for adults, or seating position, which is the preferred position for children[5].

Like any other invasive procedure, it can be painful; that is why a local anaesthetic can be used, such as subcutaneous mepivacaine or topical anaesthetic preparations[6]. In paediatric patients, it could be necessary to use pharmacological sedation. The SECIP (Spanish Society for Paediatric Intensive Care) recommends the administration of midazolam in combination with ketamine or fentanyl for this indication[7].

When the LP is conducted as a diagnostic procedure, a specific amount of CSF will be extracted; it is recommended to restrict this to the lowest volume necessary, which is usually 6-8 mL in adults, 2-3 mL in newborns and infants, and 5-8 mL in children and adolescents. If the LP is conducted as a therapeutic procedure, the drug will be slowly introduced after extracting the relevant volume of CSF. It is recommended to conduct the administration over 3 to 5 minutes,

approximately; moreover, a slower administration is recommended in patients with small brain ventricles or high intracranial pressure, in order to avoid headaches[3,8].

There are no consistent data in scientific literature regarding the volume of drug dilution recommended for LP administration, or the CSF volume recommended for previous extraction. Overall, in order to prevent an increase in intracranial pressure when drugs are administered through the IT procedure, it is recommended not to modify the CSF volume. Therefore, it is recommended to extract, before IT administration, a CSF volume equivalent to the volume of chemotherapy to be instilled[3,8,9].

Regarding the volume of the drug to be administered, Pui recommends that the cytostatic agent must be dissolved in at least 6 mL of fluid, in order to achieve its adequate distribution[10]. The British Columbia Cancer Agency (BCCA) recommendations also recommends 6 mL as the volume of IT drug administration for adults[8]. For children, different authors have described administration volumes ranging from 6 mL for <1-year-old to 12 mL for ≤3-year-old[11,12]. The AHFS Drug Information states that it is usual to extract a CSF volume similar as the one to be injected: from 5 to 15 mL[13]. In general, it is considered that a CSF volume of 7 to 10 mL must be extracted in adults, and a similar volume of intrathecal chemotherapy must be instilled[3].

After drug administration, it is recommended that patients should stay at least 1 hour in prone position, in order to facilitate the penetration of the chemotherapy agent in the brain ventricles[14]. Other authors recommend staying from 1 to 12 hours in supine position, to avoid the risk of post-puncture headache[15].

Some of the complications that can appear after LP, even if conducted for diagnosis, are: development of post-puncture headache, lower back pain, nerve root irritation, infections or haemorrhages, among others[16].

Ommaya *Reservoir*

The *Ommaya* Reservoir is an intraventricular device, which is placed in the subcutaneous scalp tissue, with a catheter inserted in one of the lateral ventricles of the brain, and thus connected with CSF circulation. It is recommended for use in those patients who require frequent or prolonged CNS treatments or for those cases where LP would represent a difficult technique[3].

Medications are injected with a syringe in the ventricular reservoir. The way of administration varies depending on the source. Some sources recommend the gradual extraction of 12 to 20 mL of CSF, at a rate <1-2 mL/ minute, with a syringe size <10 mL. After CSF extraction, the medication will be infused at a 1 mL/minute rate. Afterwards, approximately 10 mL of the previously extracted CSF will be re-infused, in order to clean the *Ommaya* needle and catheter[3]. Other sources recommend extracting a CSF volume similar to the volume of drug to be

administered, and cleaning with 3-4 mL of 0.9% sodium chloride solution 0.9% after administration[8].

The implantation of the *Ommaya* Reservoir exposes patients to a 5-10% risk of suffering complications, including haemorrhage, infection, and complications associated with device malfunctioning[17].

Despite the risks associated with device implantation, the main advantage of the *Ommaya* Reservoir over LP, is a more homogeneous drug distribution in the subarachnoid space. The drug concentration in the ventricular CSF after LP administration is only 10% of that immediately achieved after the intraventricular administration of an equivalent dose of drug[18]. Moreover, various studies have demonstrated that the distribution in the brain ventricles of drugs administered through LP is influenced by the position after puncture; therefore, a >10 times higher reduction in concentration could occur if the patient does not stay lying down during 1 hour after administration[14].

*General characteristics of preparations for intrathecal administration*

Drugs for IT administration must meet some requirements for their preparation and formulation, which are recommended according to CSF characteristics (Table 1). The nervous tissue is particularly sensitive to any physical or chemical aggression; and therefore, according to various authors, some factors such as pH, ionization level, or the presence of antibacterial agents during preparation, can be associated with the toxicity of the drug administered[19]. In general terms, solutions for IT administration must be[9,20]: sterile, apyrogenic, limpid, isoosmotic with CSF, with a pH close to the CSF´s ph, and without preservatives.

Taking these characteristics into account, formulations for intrathecal use must be prepared in laminar flow cabinets, to ensure their sterility and avoid the presence of contaminating and pyrogenic agents. Besides, as stated by Gil and col., it is recommended to filter the preparation through a 0.22 membrane filter, to eliminate any potential particles generated during preparation[9].

Regarding osmolarity and pH, Elliott B (EB) solution was marketed in U.S.A. during some years; it was indicated for the IT administration of cytarabine and methotrexate, and was comparable with CSF in terms of osmolarity (288 mOsm/L), pH (6.5 to 7), electrolytic composition and glucose contents. A lower incidence of adverse effects was described, associated with the IT administration of drugs prepared in this vehicle *vs.* 0.9% sodium chloride solution or sterile water for injection[21]. There is no solution with these characteristics currently in the market, but it is recommended that the osmolarity and pH of the preparations for intrathecal administration should be close to CSF values, with the objective of improving their tolerability.

In terms of the presence of preservatives, many of the multiple-dose formulations commonly used contain preservatives such as benzyl alcohol and methylparaben or propylparaben. There have been reports of

adverse events caused by the intrathecal administration of benzyl alcohol, such as paraparesis, nerve root demyelination, and horsetail fibrosis[22]. There is lower experience with parabens, and no adverse events have been described associated with their intrathecal administration; however, there are reports of anaphylactic reactions secondary to their intravenous administration, and this risk, together with the few data available about their IT administration, avoid their IT administration. Thus, it is considered in practice that all drugs for IT administration should be preservative-free[23]; therefore, before the intrathecal administration of any medication, it should be confirmed that it does not contain preservatives, taking into account that different medicinal products of the same drug can have different formulations.

*Intrathecal Chemotherapy*

The drugs most traditionally used for intrathecal administration in neoplastic conditions in general, and specifically for haematological conditions, have been methotrexate, cytarabine, and glucocorticoids[24-27]; these drugs are often used in combination in the called TIT therapy. More recently, liposomal formulations of cytarabine[29] have been introduced, and even monoclonal antibodies have been administered this way: rituximab for lymphoma[29], and trastuzumab for brain metastasis in HER2+ breast cancer[30].

*Methotrexate*

The pharmacokinetic of methotrexate (MTX) is different for IT administration and systemic administration. The elimination of MTX from the CSF depends mainly on the CSF flow (because there is no active transportation from CSF to blood, and MTX is not metabolized in the CSF); it has an initial elimination half-life ($t_{½}$) of 4.5 hours, and a final $t_{½}$ of 14 hours, and is reduced to sub-therapeutical concentrations 4 days after IT administration[31].

Even though IT MTX is widely used, its optimal dose has not been clearly established; but it has been demonstrated that dose calculation based on weight or body surface is inadequate. Bleyer and col. proved that the administration of IT MTX doses based on body surface increased neurotoxicity in adolescent and adult patients, because very high MTX concentrations were reached in the CSF[31]. The reason for this, as we have already mentioned, is that there is a fast increase in the CSF volume during the first years of life, and the volume in ≥3-year-old children is equivalent to the volume in adults. Therefore, it is clearly defined that the calculation of MTX doses must be conducted according to age[31], but the IT MTX dose in different studies ranges generally from 10 to 15 mg [13,24-25,32-39], and is lower in <2-year-old patients (Table 2).

**Table 2**

*Intrathecal methotrexate doses in monotherapy used according to different authors*

| Study | Condition | Indication | Age | MTX dose |
|---|---|---|---|---|
| Franklin and col.[24] | Haematological malignancies | Prophylaxis | 1 to 2-year-old<br>2 to 3-year-old<br>3 to 8-year-old<br>≥9-year-old | 8mg<br>10mg<br>12mg<br>15mg |
| Bleyer and col.[31] and AHFS Drug Information[13] | Haematological malignancies | Prophylaxis and Treatment | < 1-year-old<br>1 to 2-year-old<br>2 to 3-year-old<br>≥3-year-old | 6mg<br>8mg<br>10mg<br>12mg |
| Kim et al[32] | Solid tumour | Treatment | ≥18-year-old | 15mg |
| Kantarjian and col.[33] | ALL | Prophylaxis | ≥18-year-old | 12mg |
| Cortes and col.[34] | ALL | Prophylaxis | ≥18-year-old | 12mg |
| Mahoney and col.[35] and Matloub and col.[25] | ALL | Prophylaxis | < 2-year-old<br>2-to-3-year-old<br>≥3-year-old | 8mg<br>10mg<br>12mg |
| Siegal and col.[36] | Solid tumour and lymphoma | Treatment | ≥18-year-old | 12mg |
| Kiewe and col.[37] | Primary CNS lymphoma | Treatment | ≥18-year-old | 15mg |
| Omura and col.[38] | ALL | Prophylaxis | ≥18-year-old | 10mg/m² |
| Hill and col.[39] | ALL | Prophylaxis | <1-year-old<br><2-year-old<br>≥3-year-old | 7.5mg<br>10mg<br>12.5mg |

*Abbreviations: ALL: Acute Lymphoblastic Leukemia; MTX: Methotrexate; CNS: Central Nervous System

IT administration of MTX can cause acute, sub-acute or long-term neurotoxicity. The most frequent adverse effect is aseptic meningitis or chemical arachnoiditis, which appears approximately in 10% of the patients, though incidences of up to 50% have been described. Its characteristic symptoms are headache, nausea, and neck stiffness[40]. The concomitant administration of IT or oral corticosteroids can reduce the risk of its development. Geiser and col.[21] observed, in a cohort of paediatric patients who received IT MTX, a lower frequency in the development of chemical meningitis symptoms in those patients for whom EB solution was used as vehicle; this was attributed to the pH of this solution, closer to the physiological pH of CSF than those of other vehicles used in this study.

There have also been reports of dizziness, convulsions, sub-acute encephalopathy or leukoencephalopathy[40]. Leukoencephalopathy can appear months or years after the administration of methotrexate, and the risk is higher for those patients who are receiving concomitant CNS radiation and high doses of IV MTX[41].

*Cytarabine*

The pharmacokinetic data available for cytarabine were obtained by Zimm and col.[42], who injected intraventricularly a single 30 mg dose of cytarabine (ARA-C) to seven patients with leukemic meningitis in complete remission. After the injection, a maximum ARA-C concentration >2000μmol/L was reached in the ventricular CSF, and a <1μmol/L concentration was sustained during at least 24 hours. The ARA-C by IV administration is rapidly eliminated from plasma through the cytidine deaminase enzyme, which metabolizes ARA-C into uracil arabinoside; however, the concentration of the enzyme in the CSF

is insignificant, and this metabolic pathway won't practically occur[43]. Moreover, the value of ARA-C clearance from the CSF (0.42 mL/minute) is similar to the CSF formation and reabsorption rate (0.35 mL/minute), suggesting that ARA-C elimination from CSF is mainly due to CSF flow. The elimination of ARA-C from CSF is slower than from plasma, and clearance is eight times lower in CSF[44]. As MTX, there is no clearly established ARA-C dose, and its dose must be calculated also according to age rather than to body surface[24,33,34,45-47] (Table 3).

**Table 3**

*Intrathecal cytarabine doses in monotherapy used in different studies*

| Study | Condition | Indication | Age | Cytarabine dose |
|---|---|---|---|---|
| Franklin and col.[24] | Haematological malignancies | Prophylaxis | <1-year-old<br>1 to 2-year-old<br>2 to 3-year-old<br>≥3-year-old | 20mg<br>30mg<br>50mg<br>70mg |
| Katarjian and col.[33] and Cortes and col.[34] | Acute lymphoblastic leukemia | Prophylaxis | ≥18-year-old | 100mg |
| Esteva and col.[45] | Breast cancer | Treatment | ≥18-year-old | 100mg |
| Fulton and col.[46] | Solid tumour | Treatment | ≥18-year-old | 20mg |
| Fleischhack and col.[47] | Haematological malignancies | Prophylaxis and Treatment | <1-year-old<br><2-year-old<br><3-year-old<br>≥3-year-old | 20mg<br>26mg<br>34mg<br>40mg |

The adverse effects described with the IT administration of ARA-C are: transverse myelopathy, aseptic me ningitis, encephalopathy and convulsions; however, their development will be infrequent[24,48,49].

*Liposomal Cytarabine*

A liposomal formulation (Depocyte®) has been developed in order to enable a lower frequency of IT ARA-C administration; this is a controlled release formulation for aqueous cytarabine, which is encapsulated in spherical and multivesicular particles called DepoFoam®, which present a longer half-life of CSF elimination. With this formulation, a two-phase elimination profile has been described, with a terminal stage $t_{½}$ within 100 and 263 hours, for a dose range between 12.5 mg and 75 mg; on the other hand, standard-release cytarabine presents a terminal stage $t_{½}$ of approximately 3.4 hours for 30mg doses[50]. After the IT injection, the liposomal particles containing the ARA-C will break down, and the lipids will enter the normal metabolic pathways of the body. In 2007, Phuphanich and col. studied the pharmacokinetics of Depocyte® by administering 2 intraventricular or intralumbar doses to 8 patients, separated by a 14-day interval, and taking samples at different points up to 14 days after administration. The concentration of free and encapsulated ARA-C in the ventricular and lumbar CSF varied from 0.01 to 1500μmol/L, and was detectable during 14 days post-dose. Systemic exposure to cytarabine was considered non-significant[28].

The efficacy of IT liposomal cytarabine has been demonstrated in two controlled and randomized clinical trials, in patients with neoplastic meningitis associated with lymphoma and solid tumours *vs.* conventional

IT cytarabine and IT methotrexate, respectively[51,52]. In the clinical trial conducted *vs.* conventional ARA-C, a higher response rate was observed in the liposomal cytarabine group; however, there were no statistically significant differences in duration of response, progression-free survival and overall survival. In the clinical trial conducted *vs.* MTX, progression-free survival was also similar with the two agents.

Opposite to methotrexate and standard-release cytarabine, the dose of liposomal cytarabine in adults has been defined as 50mg with IT administration, in a 5 mL volume; the dosing interval varies according to the treatment stage. The indication approved for Depocyte® by the Spanish Agency of Medicines and Medical Devices is the treatment of lymphomatous meningitis[50].

The toxicity of liposomal cytarabine is relatively high, particularly when administered in association with other drugs which cross the BBB. In the M.D. Anderson Centre for Cancer Treatment, a study was conducted on adults diagnosed with ALL and treated with the Hyper-CVAD regimen, which includes high-dose IV MTX and ARA-C. The introduction of IT liposomal cytarabine was associated with a higher toxicity rate (16%), including encephalopathy, cauda equina syndrome, convulsions, and *pseudotumor cerebri*. The conclusion was that severe neurotoxicity could be caused by the concomitant administration of liposomal cytarabine and drugs that can cross the BBB or radiotherapy[53]. In the randomized clinical trial comparing the ARA-C liposomal and standard formulations, conducted by Glantz, the majority of the adverse effects were transitory. The only effect that appeared in over 10% of treatment cycles was headache, which was more frequent in the liposomal cytarabine group than in the traditional cytarabine group (27% *vs.* 2%). Chemical arachnoiditis appeared in 22% of patients treated with liposomal cytarabine *vs.* 13% of patients treated with the standard formulation[52]. In order to reduce the incidence of arachnoiditis, it is recommended to administer systemic dexamethasone during 5 days, initiating treatment on the same day of the IT injection.

*Glucocorticoids*

Even though intrathecal administration of glucocorticoids is common, its pharmacokinetics in the CNS has not been clearly documented. Balis and col[54]. studied the activity of dexamethasone and prednisolone in the CSF in a non-human primate model, after its intravenous and intraventricular administration. Both drugs are rapidly cleared from CSF after intraventricular administration; however, after intravenous administration, there is low penetration in the CSF due to the high binding to plasmatic proteins in both, though dexamethasone presents higher penetration due to its lower binding to plasmatic proteins (70% for dexamethasone *vs.* 90% for prednisolone).

IT glucocorticoids are mostly used in combination with ARA-C and MTX. This concomitant use has two objectives: increasing the effectiveness of IT therapy, and reducing the incidence of meningeal irritation[23]. There is wide evidence about the use of corticosteroids as

part of intrathecal treatment in oncohaematology; in 1983, Muriel and col[55]. used IT methotrexate 12mg/m² (maximum dose = 15 mg) and dexamethasone 14mg/m², and in 1995, Gómez-Almaguer administered IT dexamethasone 5mg/m² diluted in 5mL of 0.9% sodium chloride with MTX and ARA-C together in 8 patients with ALL and leukemic infiltration in their CNS; the cell count was reduced in CSF after the administration of combined intrathecal chemotherapy in all patients[56]. However, the use of corticosteroids with IT chemotherapy is not universal: its use, the one used, and its dose will vary according to the protocols of the different study groups. Overall, its use is more widespread for the treatment of paediatric patients than for adults.

The International Berlin-Frankfurt-Munster (BFM) Study Group[57,58], in its protocols for ALL treatment in children, uses prednisolone as corticosteroid for IT administration, recommending doses that vary according to age: <1-year-old: 6mg, 1 year-old: 8 mg, 2-year-old: 10 mg, and ≥3-year-old: 12mg. Thus, the BFM Study Group recommends the use of prednisolone with MTX and ARA-C for prophylaxis and treatment of meningeal infiltration in ALL. This is also the corticosteroid used in the Japanese JALSG-ALL93 protocol for adults with ALL, with doses of 10mg[59].

The Italian GIMEMA group has used IT MTX 12mg with methylprednisolone 40mg for ALL treatment in patients from 12 to 60-year-old[60]. The dose of 40mg of methylprednisolone for adult patients with ALL has also been used with MTX 15mg and ARA-C 40mg by the French LALA Group[61], and in the GRAALL-2003 Protocol[62].

In U.S.A., the use of intrathecal corticosteroids for ALL treatment in adult patients has not become widespread; thus, it is not included in the CALGB-8811 study[63] or in the studies conducted by Katarjian[33] and Rowe[64], where IT MTX 15 mg, 12 mg and 12.5 mg is used for CNS prophylaxis, respectively. However, for paediatric patients with ALL, both the Pediatric Oncology Group and the Children's Oncology Group use hydrocortisone with MTX and ARA-C dosed according to age[25,35]. The protocols for treatment and prophylaxis of CNS infiltration in acute leukemia in children from the St. Jude's Children's Research Hospital also use hydrocortisone as part of the TIT therapy at 16 mg, 20 mg or 24 mg doses, based on age (<1 year-old, 2-3-year-old or ≥3-year-old, respectively)[65].

The PETHEMA Group (Program for the Study and Treatment of Haematological Malignancies) and the Spanish Society of Paediatric Haematology and Oncology (SEHOP) indicate the use of hydrocortisone (HC) with ARA-C and MTX in the majority of their protocols for ALL treatment, recommending this dosing: <2 year-old: 10 mg, 2-3-year-old: 15 mg, ≥3-year-old: 20 mg[66]. However, other protocols from the PETHEMA Group have incorporated the use of dexamethasone. For example, Burkimab-13, widely used in Spain for the treatment of Burkitt Lymphoma in adult patients, indicates the use of MTX 15mg in combination with ARA-C 40 mg and dexamethasone 4

mg[67] for prophylaxis and treatment of CNS infiltration. PETHEMA-LAL-07OLD also uses IT dexamethasone 4 mg with MTX and ARA-C[68].

The toxicity of the intrathecal administration of glucocorticoids has not been studied yet by controlled studies; in fact, its use in combination with IT chemotherapy is associated with a reduction of the adverse effects, primarily the development of chemical arachnoiditis. However, the development of psychiatric adverse effects caused by the use of intrathecal corticosteroids has been described in various studies; it can be ranged from depressive syndromes to psychosis[69]. In the study conducted by Hitchins, where IT hydrocortisone was administered before the administration of IT chemotherapy, two unusual reactions were observed in two patients, who experienced headache, vomiting and confusion, in both cases after the administration using the *Ommaya* reservoir. These symptoms disappeared spontaneously a few hours after administration. When both patients were re-treated with IT hydrocortisone, they suffered the same reaction again; when the administration of IT hydrocortisone was removed from the rest of the administrations of IT chemotherapy, this reaction did not appear again when chemotherapy was administered alone. The authors did not find an explanation for these reactions[70].

*Monoclonal Antibodies: Rituximab and Trastuzumab*

There has been recent research into the administration of two monoclonal antibodies; this represents an innovative targeted therapy for the treatment of leptomeningeal carcinomatosis: trastuzumab for HER2 positive breast cancer, and rituximab for the treatment of B-cell lymphoma.

Trastuzumab is highly effective in the treatment of breast cancer with HER2 overexpression; however, despite its efficacy, patients treated with trastuzumab and chemotherapy will experience an incidence of CNS metastasis ranging from 28% to 42%[30]. Stemmler and col. observed that the concentration of trastuzumab in the CSF after intravenous administration was 300 or 400 times lower than its concentration in plasma[71]; therefore, in order to achieve therapeutic concentrations of trastuzumab in the CSF, it has been considered to use IT administration. This drug has been used in series of cases, alone or in combination with intrathecal methotrexate or thiotepa, at doses between 12.5 and 25 mg administered with a frequency ranging from 3 days to 3 weeks. The most typical regimen used was 20-25 mg once a week, and all dosing regimens were well tolerated. With these regimens, there have been responses at CSF level and even an increase in survival without toxic effects[30].

Rituximab is an anti-CD20 antibody; over 90% of B-Cell Non-Hodgkin lymphomas (NHL) and primary CNS lymphomas express the CD20 marker, but healthy brain tissue does not express it. Like trastuzumab, rituximab has a low penetration in the CSF; its concentration in CSF after systemic administration represents 0.1% of concentrations in blood serum. Rubenstein and col[29]. conducted a

Phase I clinical trial on 10 patients with B-cell NHL and primary CNS lymphoma with neoplastic meningitis, who were administered rituximab through an *Ommaya* Reservoir, every week during the first week of the study, and then twice a week during 4 weeks. The doses used for rituximab were 10 mg, 25 mg and 50 mg, and toxic effects appeared with the 50 mg dosing (hypertension, nausea, vomiting and double vision). The median survival was 21 weeks, six patients experienced meningeal response, and two of the three patients with intraocular disease experienced a local response. The combination of liposomal cytarabine with IT rituximab was tested by Chamberlain and col. in 14 patients with lymphoma and relapsing neoplastic meningitis. Each patient was administered an induction regimen including 25 mg of IT rituximab twice a week and liposomal cytarabine every 14 days, during 4 weeks. A maintenance stage was then conducted, including 50 mg of liposomal cytarabine and two doses of rituximab 25 mg administered in the same week, every 4 weeks, until disease progression. After the induction regimen, 10 patients experienced partial neurological response, and received maintenance therapy. The probability of survival at 6 months was 29%, and toxic effects were moderate and expected, probably due to liposomal cytarabine[72].

There is lack of information about the way in which monoclonal antibodies should be prepared and administered for intrathecal administration; logically, the requirements for preparation for intrathecal use must be considered, always in a sterile and apyrogenic setting, and using disolvents preservatives-free[20]. In the case of trastuzumab, only one of the publications explained how it had been prepared: the usual reconstitution process (150 mg in 7.2 ml water for injection; pH 6), and administration of the adequate volume (20 mg in 0.95 mL), without additional dilution[73]. For rituximab, one of the studies specified that it had been prepared by diluting rituximab with 0.9% sodium chloride solution on a 1:1 ratio for 10 and 25 mg doses, and without dilution for 50mg doses, and administered over 1 to 5 minutes[72].

It has not been established if intraventricular or intralumbar administration has any influence on the results.

*Intrathecal Triple Chemotherapy*

The use of IT combination chemotherapy is a logical consequence, because it has been demonstrated that the use of combination systemic chemotherapy increases efficacy when compared *vs.* the individual administration of antineoplastic agents. That is why many research groups advocate for the use of TIT chemotherapy, which consists in administering methotrexate, cytarabine and a glucocorticoid in combination[26]. The use of these three agents in combination could have an additive or synergic effect for the prophylaxis and treatment of neoplastic meningitis.

In Spain, the use of TIT for the prophylaxis and treatment of the leukemic CNS involvement and certain NHLs is the most widespread practice, because it is the treatment indicated in the protocols promoted by the PETHEMA Group[74] and SEHOP[75]. The habitual use of this

strategy in adults is shown in the outcomes of the studies conducted by the QUIT (Spanish Registry of Patients receiving Intrathecal Chemotherapy)[74,76].

The efficacy of TIT therapy *vs.* MTX monotherapy was comparable in the study conducted by the Southwest Oncology Group, which included paediatric patients diagnosed with ALL and active meningeal disease (com plete response rate of 96% *vs.* 100%)[27] In the CCG-1952 clinical trial, children with standard-risk ALL were randomized to receive MTX alone (n=1018) or TIT (MTX, ARA-C and HC, n=1009) for prophylaxis of leukemic CNS involvement. Compared with IT MTX, TIT significantly reduced the risk of relapse in CNS (3.4%±1.0% *vs.* 5.9%±1.2%, p=0.004); however, the survival free of disease at 6 years was equivalent between both treatment groups (80.7%±1.9% *vs.* 82.5% ±1.8%, p=0.3), due to a higher proportion of bone marrow and testicular relapses, which was associated with a significant reduction in overall survival (Survival at 6 years: TIT 90.3% *vs.* IT MTX 94.4%, p=0.01)[25].

No direct comparisons have been published for the use of IT liposomal cytarabine *vs.* TIT therapy.

The adverse effects due to the use of TIT therapy are not qualitatively different from those previously described with IT MTX and ARA-C, and from the risks associated with the administration technique itself (LP or intraventricular). The most common adverse effects are headaches, nausea, vomiting and fever; more severe adverse effects will occur less frequently, such as chemical arachnoiditis, loss of vision, and leukoencephalopathy([24,77)].

As we have mentioned previously, the use of corticosteroids in combination with IT chemotherapy seems to have a beneficial effect on the profile of adverse events; because the risk of meningeal irritation, described with the IT administration of MTX and ARA-C in monotherapy, will be reduced with the concomitant IT administration of a corticosteroid[78].

As well as the IT administration of drugs in monotherapy, the doses of TIT to be administered are not clearly defined. However, there is consensus regarding the need to calculate the dose based on age and not on body surface. The MTX, ARA-C and HC doses used in different studies[11,12,24,25,35,64,65,79-82] are shown in Table 4.

**Table 4**
*Dose of Intrathecal Triple Chemotherapy (methotrexate, cytarabine and hydrocortisone) based on age, in different studies*

| Study | Age | MTX dose (mg) | ARA-C dose (mg) | HC dose (mg) |
|---|---|---|---|---|
| Liu and col.[12] and Lin and col.[11] | <1-year-old | 6 | 12 | 6 |
| | 1 to 2-year-old | 8 | 16 | 8 |
| | 2 to 3-year-old | 10 | 20 | 10 |
| | >3-year-old | 12 | 24 | 12 |
| Franklin and col.[24] | ≤1 year-old | 7.5 | 15 | 7.5 |
| | 1 to 2-year-old | 8 | 16 | 8 |
| | 2 to 3-year-old | 10 | 20 | 10 |
| | 3 to 8-year-old | 12 | 24 | 12 |
| | ≥9-year-old | 15 | 30 | 15 |
| Matloub and col.[25] | <2-year-old | 8 | 16 | 8 |
| | 2 to 3-year-old | 10 | 20 | 10 |
| | 3 to 8-year-old | 12 | 24 | 12 |
| | >8-year-old | 15 | 30 | 15 |
| Mahoney and col.[35] | 1-year-old | 8 | 16 | 8 |
| | 2-year-old | 10 | 20 | 10 |
| | ≥3 to 8-year-old | 12 | 24 | 12 |
| | ≥9-year-old | 15 | 30 | 15 |
| Pui and col.[65] | <2-year-old | 8 | 24 | 16 |
| | 2 to 3-year-old | 10 | 30 | 20 |
| | ≥3-year-old | 12 | 36 | 24 |
| Ortega and col.[66] | <12 month-old | 5 | 16 | 10 |
| | 12-to-23-month old | 8 | 16 | 10 |
| | 24-to-35-month old | 10 | 20 | 15 |
| | ≥35-month old | 12 | 30 | 20 |
| Ruggiero and col.[79] | <2-year-old | 8 | 16 | 8 |
| | <3-year-old | 10 | 20 | 10 |
| | ≥3-year-old | 12 | 24 | 12 |
| Tomizawa and col.[80] | <2-year-old | 7.5 | 15 | 15 |
| | <3-year-old | 10 | 20 | 20 |
| | ≥3-year-old | 12.5 | 25 | 25 |
| LAL SEHOP/PETHEMA 2013[81] | 12-to-23-month old | 8 | 16 | 10 |
| | 24-to-35-month old | 10 | 20 | 15 |
| | ≥35-month old | 12 | 30 | 20 |
| Ribera and col.[82] | 15-to-60-year-old | 12 | 30 | 20 |

Other studies and work groups have used TIT with dexamethasone, prednisone or methylprednisolone, as mentioned in the section for intrathecal glucocorticoids. The TIT therapy used by the BMF Study Group was: MTX <1-year-old: 6 mg, 1-year-old, 8 mg, 2-year-old, 10 mg, ≥3-year-old: 12 mg; for ARA-C, <1-year-old: 15 mg, 1-year-old: 20 mg, 2-year-old: 25 mg, ≥3-year-old: 30 mg; for prednisolone: <1-year-old: 6 mg, 1-year-old: 8 mg, 2-year-old: 10 mg, ≥3-year-old: 12 mg[57,58]. Combinations at variable doses have also been described for adult patients[61-64,67,68].

There are no studies comparing the efficacy and/or toxicity of the different TIT preparations, and therefore there is uncertainty regarding the adequacy of combinations. In fact, there is no knowledge about the equivalent potential for different corticosteroids with IT administration, and the doses used in different protocols would not be equally potent, using the criteria typically accepted for systemic administration[83].

As the lack of homogeneity in dosing, the disolvent used and the administration volume are not described in almost any study; and according to various authors, these are factors that can have impact on

tolerability to treatment and in the adequate distribution of the drug in the CSF[12].

Of all the studies shown in Table 4, only Liu and col.[12] and Lin and col.[11] have described the volume used, which varied according to age, and was in both studies: <1-year-old: 6 mL, 1-2-year-old: 8 mL, 2-3-year-old: 10 mL, and ≥3-year-old: 12 mL. Lin and col.[11] stated that they had used the dilution volume adequate to increase the efficacy of TIT therapy, though there was no argument supporting this claim.

Sullivan and col., in a study comparing the efficacy and toxicity of TIT therapy *vs.* methotrexate and hydrocortisone, commented that the solvent used for preparation was EB solution, however the dilution volume was not named[27]. They also described that the IT administration of the 3 drugs was sequential: MTX was administered first, followed by HC and finally ARA-C[27]. This description of sequential administration is exceptional, because in the majority of the studies it is not stated whether the administration is conducted with the total mixture in one single syringe or in separated syringes for each agent and, in this case, the order for the administration.

Currently, the most accepted trend is to mix the three components in one single syringe, to facilitate IT administration and prevent excessive handling (connecting and disconnecting the catheter), thus reducing the risk for accidental contamination during administration.

The ALL SEHOP / PETHEMA 2013 paediatric protocol describes the preparation and administration of IT treatment. It states that the 3 cytostatic agents must be administered in the same syringe, and that doubly distilled water must be used for the reconstitution of cytarabine and hydrocortisone, which will be sterile, apyrogenic and preservatives-free; the volume will then be completed with 0.9% sodium chloride solution. This protocol recommends a pH and osmolarity for the preparation of 7.3 pH and a 300 mOsm/l, respectively[81].

Besides the aspects considered, another important issue when using drug mixtures is to ensure the physicochemical stability of the final preparation. There are few stability studies for TIT preparations, and the majority have been conducted with EB solution. The most recently published study evaluates the stability of sodium methotrexate, cytarabine and hydrocortisone sodium phosphate in a 0.9% sodium chloride solution, with pH and osmolarity adjusted to values close to the CSF ph; the conclusion was that the TIT preparations evaluated were chemically stable during at least 7 days at room temperature (RT), and under refrigeration; however, the pH of the preparations was out of the physiological values of CSF at 5 days in the preparations stored with refrigeration, and at 2 days in those stored at RT[84]. The characteristics of the studies conducted[19,84-87] are shown in Table 5.

**Table 5**
*Summary of the stability studies for TIT*

| Study | Drugs | Conditions | Disolvent | Study duration | Conclusion |
|---|---|---|---|---|---|
| Cradock and col.[19] | MTX, ARA-C and HCSS not mixed | 22°C and 30°C | EB, SCh, RL | 168 hs. | MTX and ARA-C stable 7 days at 22°C and 30°C. HCSS stable 72 hs. in RL and SCh, and 24 hs. in EB. |
| Olmos-Jiménez and col.[84] | MTX, ARA-C and HCSPh | 2-8°C and 25°C | SCh (with $NaHCO_3$) | 168 hs. | Chemically stable mixtures for 168 hs at 2-8°C and 25°C |
| Zhang and col.[85] | MTX, ARA-C and HCSS not mixed | 4°C and 23°C | EB | 48 hs. | MTX and ARA-C stable 48 hs. at 4°C and 23°C. HCSS stable 48 hs. at 4°C and 24 hs. at 23°C |
| Trissel and col.[86] | MTX and ARA-C with or without HCSS. | 4°C and 23°C | EB | 48 hs. | Preparations stable 48 hs. at 4°C and 23°C |
| Cheungh and col.[87] | MTX, ARA-C and HCSS | 25°C | EB, SCh, RL, Dx | 24 hs. | Preparations stable in all disolvents >24 hs, except for HCSS in EB 1.25 mg/mL. |

**Abbreviations:** ARA-C: cytarabine; EB: Elliot B Solution; hs: hours; HCSPh: hydrocortisone sodium phosphate; HCSS: hydrocortisone sodium succinate; $NaHCO_3$: sodium bicarbonate; MTX: methotrexate; RL: ringer's Lactate; SCh: 0.9% sodium chloride; Dx: dextrose 5%.

Abbreviations: ARA-C: cytarabine; EB: Elliot B Solution; hs: hours; HCSPh: hydrocortisone sodium phosphate; HCSS: hydrocortisone sodium succinate; NaHCO3: sodium bicarbonate; MTX: methotrexate; RL: ringer's Lactate; SCh: 0.9% sodium chloride; Dx: dextrose 5%.

There are few stability studies for TIT preparations with corticosteroids other than hydrocortisone. The Burkimab-13 protocol[67], which indicates the use of TIT with methotrexate, cytarabine and dexamethasone, recommends administering dexamethasone in a separate syringe from methotrexate and cytarabine, due to the lack of evidence on the stability of this preparation, because there are no studies on the stability of TIT mixtures with dexamethasone as a corticosteroid. The same protocol recommends replacing dexamethasone by hydrocortisone, if it is preferred to administer the IT chemotherapy in one single syringe.

In 2012, D'Hont and col. conducted a stability study for ARA-C, MTX and methylprednisolone in 0.9% sodium chloride solution during 48 hours. The conclusion was that the preparation was stable up to 12 hours when stored at 5°C and protected from light[88].

In 2014, the Ministry of Health, Social Services and Equality, together with the Spanish Society of Hospital Pharmacy, published guidelines for good practice in the preparation of medications in Hospital Pharmacy Units, where sterile preparations were classified according to a risk matrix. These guidelines classified the preparations for IT administration as high-risk preparations, and the following preparation requirements were defined: preparation in a laminar flow cabinet with controlled environment (clean room), and as storage requirements: a maximum storage time of 24 hours at RT and 3 days at a 2-8°C temperature[89-90].

## Conclusions

There is a wide variability in practice when using IT chemotherapy, despite being an effective therapy, accepted by all international groups, particularly for the treatment of acute leukemia and Non-Hodgkin

lymphomas. This variability and uncertainty is not limited to the drugs and doses administered, but it also includes the way of preparation and the administration technique.

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## Conflict of interest declaration

Conflict of Interests

There is no conflict of interests.