HDMTX en tumores sólidos y hematológicos: Rescate.

Dra. A. Aldaz, Dra. M.D. Aumente,
Dr. J.L. Dapena, Dr. F.J. Bautista.

Estrategias para la mejora del tratamiento con dosis altas de metotrexato: la farmacocinética clínica como herramienta para la optimización de la eficacia y toxicidad.

19 de octubre de 2015

HDMTX en tumores sólidos y hematológicos: Rescate.

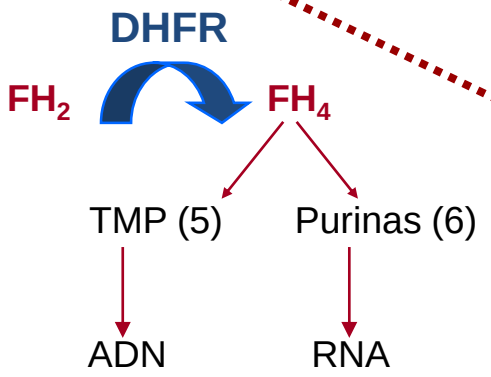
Dra. M. Dolores Aumente.

- ¿Cuándo se debe iniciar y finalizar el rescate?

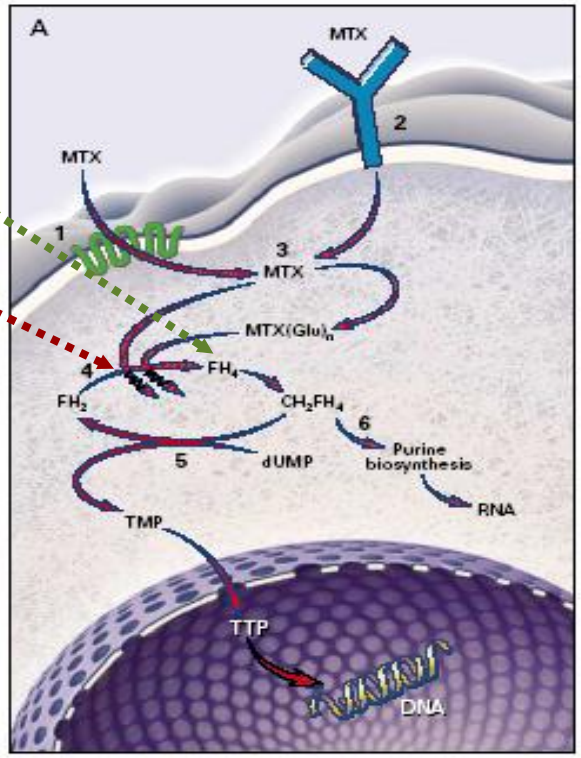
- ¿Cuál es la dosis mínima de ac. folínico?

¿Rescate? Cuando iniciar, dosis y fin…

MTX **Inhibición competitiva de la**



N^5-formil-FH_4 (Leucovorin)



Gorlick R, et al. N Engl J Med 1996; 3;335(14):1041-8.

- *Iniciar el rescate lo mas tarde posible:*
- *Administrar la mínima dosis de LV*
- *Suspender el LV cuando ya no sea necesario*

Inicio?	**MTX en 4 horas: 24h o 30 h** **MTX en 24 horas: 36h o 42 h**
Dosis?	**10-15 mg/m²**
Fin?	**<0.1, 0.2 o 0.25µM**

Dra. Aumente

HDMTX en tumores sólidos y hematológicos: Rescate.

Dr. José Luis Dapena.

- **Riegos y beneficios de una dosis excesiva vs insuficiente de ácido folínico a corto y largo plazo en los tumores hematológicos**

Metotrexato: toxicidad

- Mielosupresión*
- Toxicidad gastrointestinal*
- Hepatotoxicidad
- Nefrotoxicidad: HDMTX: Incidencia: 1.8% (rango, 0-12%). Mortalidad en los pacientes con disfunción renal: 4.4%.
- Neurotoxicidad*

* El ácido folínico es particularmente eficaz en la prevención de la mielosupresión, la toxicidad GI y la neurotoxicidad.

Perazella MA, Moeckel GW (2010). Nephrotoxicity from chemotherapeutic agents: clinical manifestations, pathobiology, and prevention/therapy. Semin Nephrol 30:570-581

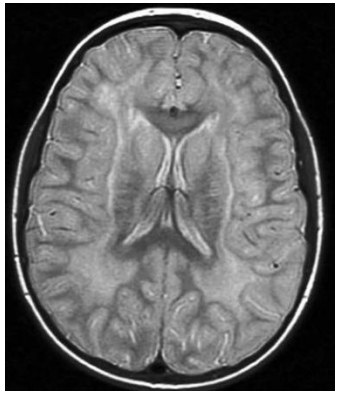
Widemann B et al. (2004). High-Dose Methotrexate-Induced Nephrotoxicity in patients with osteosarcoma. Incidence, treatment, and outcome. Cancer 100 (10): 2222-2232

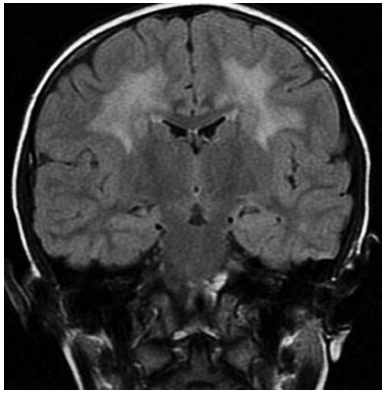
Ackland SP, Schilsky RL (1987). High-dose methotrexate: a critical reappraisal. J Clin Oncol 5:2017-2031

Neurotoxicidad por metotrexato en pacientes pediátricos. Descripción de los síntomas clínicos y hallazgos neurorradiológicos.
Montserrat García-Puig et al. Rev Neurol 2012;54 (12):712-718.

Fisiopatología: el efecto antimetabolito del MTX:

- **inhibe la DHFR** y la **síntesis del tetrahidrofolato**; se altera la síntesis de macromoléculas esenciales, incluyendo proteínas y lípidos de la mielina, e inhibición en el recambio de la mielina y la leucoencefalopatía.
- la inhibición de la DHFR lleva a la **deficiencia de S-adenosilmetionina**, importante para mantener la mielina, lo que causa desmielinización.
- la inhibición de la DHFR conlleva un **déficit de folato y carbamida**, que causa un aumento en los niveles de homocisteína, con efecto tóxico en el endotelio vascular.
- promueve la liberación de **adenosina** en los fibroblastos y células endoteliales vasculares; dilatan los vasos sanguíneos cerebrales, modifican la liberación pre y postsináptica de neurotransmisores y pueden disminuir la conexión neuronal.





Formas:

- **aguda** (<48h): somonolencia, confusión, convulsiones, aracnoiditis aguda (MTX IT)
- **subaguda** (2-14d): ACVA náuseas, visión borrosa, parálisis pseudobulbar, letargia, somnolencia y convulsiones. Mielopatía subaguda (MTX IT)
- **crónica**: variable en intensidad y puede ser progresiva: cambios en la personalidad, deterioro cognitivo, cuadriparesia espástica y convulsiones

N.º de paciente	Sexo	Edad al diagnóstico	Diagnóstico	Protocolo de QT	MTX EV [a]	MTX IT/IV [b]	Clínica	Hallazgos de la RM cerebral	Evolución
1	M	6 años	LLA-B común RE	SHOP-LLA 94	3 × 3	12 × 14 IT	Hemiparesia I, estado mioclónico	Afectación del parénquima supratentorial, cápsula interna, SB periventricular D > I	Secuelas clínicas graves; persistencia de lesiones en la RM
2	F	2 años	Meduloblastoma cerebeloso AR	SEOP < 3 años, post HIT-SKK 2000	5 × 3	2 × 6 IV	Aumento de la ataxia, mareo, hiperreflexia	Hiperintensidad en la SB periventricular	Recuperación favorable; persistencia de lesiones en la RM
3	M	3 años y 8 meses	Meduloblastoma AR	CCG99073	5 × 2	2 × 6 IV 12 × 1 IT	Inestabilidad, cefalea, dismetría ESD	Desmielinización difusa frontal, parietal	Mejoría clínica; persistencia de lesiones en la RM
4	F	14 años y 6 meses	LLA-B común AR	SHOP-LLA 99	3 ×2	12 × 4 IT	Somnolencia, hemiparesia D, afasia	Lesiones de la SB periventriculares en el centro oval D	Recuperación completa clínica y en la RM
5	M	3 años y 10 meses	LLA-B común RE	SHOP-LLA 99	3 × 3	12 × 5 IT	Somnolencia, visión doble, paresia VI par craneal I	Afectación de la SB supratentorial y hemisferios cerebelosos	Recuperación completa clínica y en la RM
6	F	5 años y 11 meses	LLA-B común RE	SHOP-LLA 2005	5 × 1	12 × 3 IT	Hemiparesia D	Normal	Recuperación completa
7	M	11 años	LLA-B común AR	SHOP-LLA 2005	3 × 4	12 × 14 IT	Hemiparesia D, afasia	Afectación de áreas de la SB frontoparietal I	Recuperación completa clínica y en la RM
8	M	6 años y 6 meses	LNH-T estadio IV	EURO-LBO2	5 × 4	12 × 10 IT	Irritabilidad, hiperreflexia	Leucomalacia supratentorial (Figs. 1 y 2)	Recuperación clínica; persistencia de lesiones en la RM
9	M	3 años y 3 meses	LLA-B común AR	SHOP-LLA 2005	5 × 3	12 × 9 IT	Hemiparesia D, afasia, somnolencia	Lesiones difusas en la SB frontal y parietal	Recuperación clínica; persistencia de lesiones en la RM

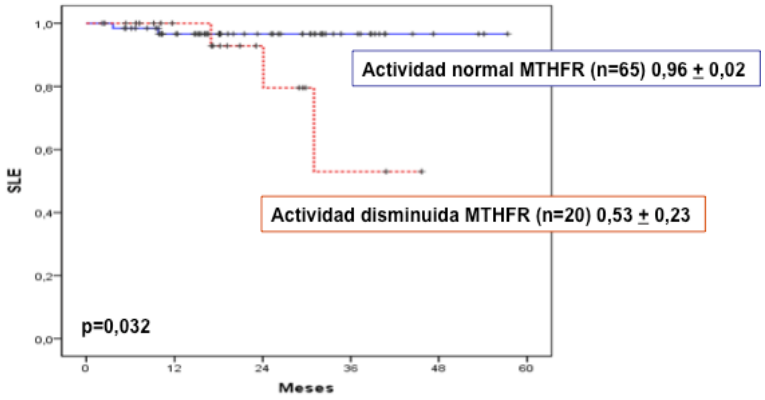
[a] mg/m² × número de infusiones endovenosas previo al inicio de la sintomatología; [b] mg × número de inyecciones intratecales/intravenosas. AR: alto riesgo; D: derecha; F: femenino; ESD: extremidad superior derecha; EV: endovenosa; I: izquierda; IT: intratecal; IV: intraventricular; LLA: leucemia linfoblástica aguda; M: masculino; LNH: linfoma no Hodgkin; MTX: metotrexato; QT: quimioterapia; RE: riesgo estándar; RM: resonancia magnética; SB: sustancia blanca.

3 pacientes con polimorfismos de riesgo de la MTHFR

Dr. Dapena

Methotrexate consolidation treatment according to pharmacogenetics of MTHFR ameliorates event-free survival in childhood acute lymphoblastic leukemia. Salazar J et al. Pharmacogenomics J. 2012 Oct; 12(5):379-85

SLE de 85 pacientes del grupo de riesgo intermedio del protocolo LAL/SHOP-2005, según actividad de la metilentetrahidrofolatoreductasa (MTHFR)



Homozigotos o dobles heterocigotos para las mutaciones 677T y/o 1298C

En el protocolo LAL/SHOP-2005 se incrementó la dosis de Metotrexato de 3 g/m^2 en 24 horas a la dosis de 5 g/m^2.
Se realizó estudio farmacogenético de la metilentetrahidrofolatoreductasa, disminuyendo la dosis de 5 a 3 g/m^2 en aquellos pacientes que eran homozigotos o dobles heterocigotos para las mutaciones 677T y/o 1298C, ya que se relaciona con una actividad disminuida de la enzima MTHFR. En la totalidad de 141 pacientes estudiados, se observó peor evolución en los pacientes con actividad disminuida y a los que según el estudio se les redujo la dosis. Este hecho fue más evidente en el grupo de riesgo intermedio en que se observó diferencia significativa. La toxicidad fue aceptable en todos los pacientes. En el protocolo en desarrollo, se ha considerado la administración a todos los pacientes de una dosis de 5 g/m^2 en infusión de 24 horas.

Dr. Dapena

Methotrexate-Induced Neurotoxicity and Leukoencephalopathy in Childhood Acute Lymphoblastic Leukemia.
Deepa Bhojwani et al. JCO. Volume 32. Number 9. March 20. 2014. 949-59

Total Therapy XV study (Junio 2000 – Octubre 2007)

- **369 pacientes:** 14 pacientes (3.8%)

Table 1. Patient Characteristics, Details of Clinical Neurotoxic Events, and Rechallenge With MTX

Patient No.	Age (years)	Sex	CNS Status*	Therapy Arm†	MTX Before Event	Time Point in Therapy	Time From MTX to Event (days)	Neurotoxic Event	Duration of Event	Subsequent No. of High-Dose MTX Doses	Subsequent No. of ITTs	Prophylaxis	Recurrent Neurotoxicity
1	13	M	CNS 2	Standard	High-dose MTX, ITT	Consolidation course one	4	Seizure (tonic clonic)	2 minutes	3	20	No	
2	3	M	CNS 1	Low	Low-dose MTX, ITT	Continuation week 40	9	Seizure (complex partial)	24 hours	0	0	NA	
3	5	M	CNS 1	Standard	High-dose MTX, ITT	Consolidation course two	3	Seizure (tonic clonic)	5 minutes	2	13	Leucovorin after ITT	
4	15	M	CNS 1	Standard	High-dose MTX, ITT	Consolidation course two	10	Stroke-like	72 hours	0 (low dose)	7	No	
5	4	M	CNS 1	Standard	ITT	Continuation week 12	7	Ataxia	4 weeks	0	8	Leucovorin after ITT	
6	10	F	CNS 1	Standard	High-dose MTX, ITT	Consolidation course three	8	Seizure (complex partial)	24 hours	1	11	Leucovorin after ITT	
7	11	M	CNS 2	Standard	High-dose MTX, ITT	Consolidation course one	11	Seizure (tonic clonic)	20 minutes	3	13	Leucovorin after ITT	
8	2	F	CNS 2	Low	Low-dose MTX, ITT	Continuation week 36	8	Seizure (complex partial)	24 hours	0	3	No	
9	16	M	CNS 1	Standard	ITT	Continuation week 13	9	Stroke-like	24 hours	0	8	Leucovorin after ITT	
10	14	F	CNS 1	Standard	High-dose MTX, ITT	Consolidation course one	7	Stroke-like	5 hours	1 (omit 2)‡	9	Aminophylline	Headache, confusion
11	5	M	CNS 1	Standard	ITT	Continuation week 29	7	Seizure (complex partial)	7 days	0	11	No	
12	12	M	CNS 1	Standard	High-dose MTX, ITT	Consolidation course one	10	Stroke-like	48 hours	3‡	11	Aminophylline	
13	18	M	CNS 1	Standard	High-dose MTX, ITT	Consolidation course one	10	Stroke-like (and seizure)	8 hours	3	20	No	Stroke (CNS thrombus)
14	17	F	CNS 1	Standard	Low-dose MTX, ITT	Continuation week 88	11	Stroke-like	36 hours	0	1	No	

Abbreviations: CSF, cerebrospinal fluid; ITT, triple intrathecal therapy; MTX, methotrexate; NA: not applicable.
*CNS1, < 5 WBC/μL of CSF without blasts; CNS2, < 5 WBC/μL of CSF with any blasts.
†Details on risk stratification described by Pui et al.[19]
‡Second high-dose MTX and ITT given 1-2 weeks apart.

- **Consulviones**: 7 pacientes; **ACVA**: 6 pacientes; **Ataxia**: 1 paciente

Dr. Dapena

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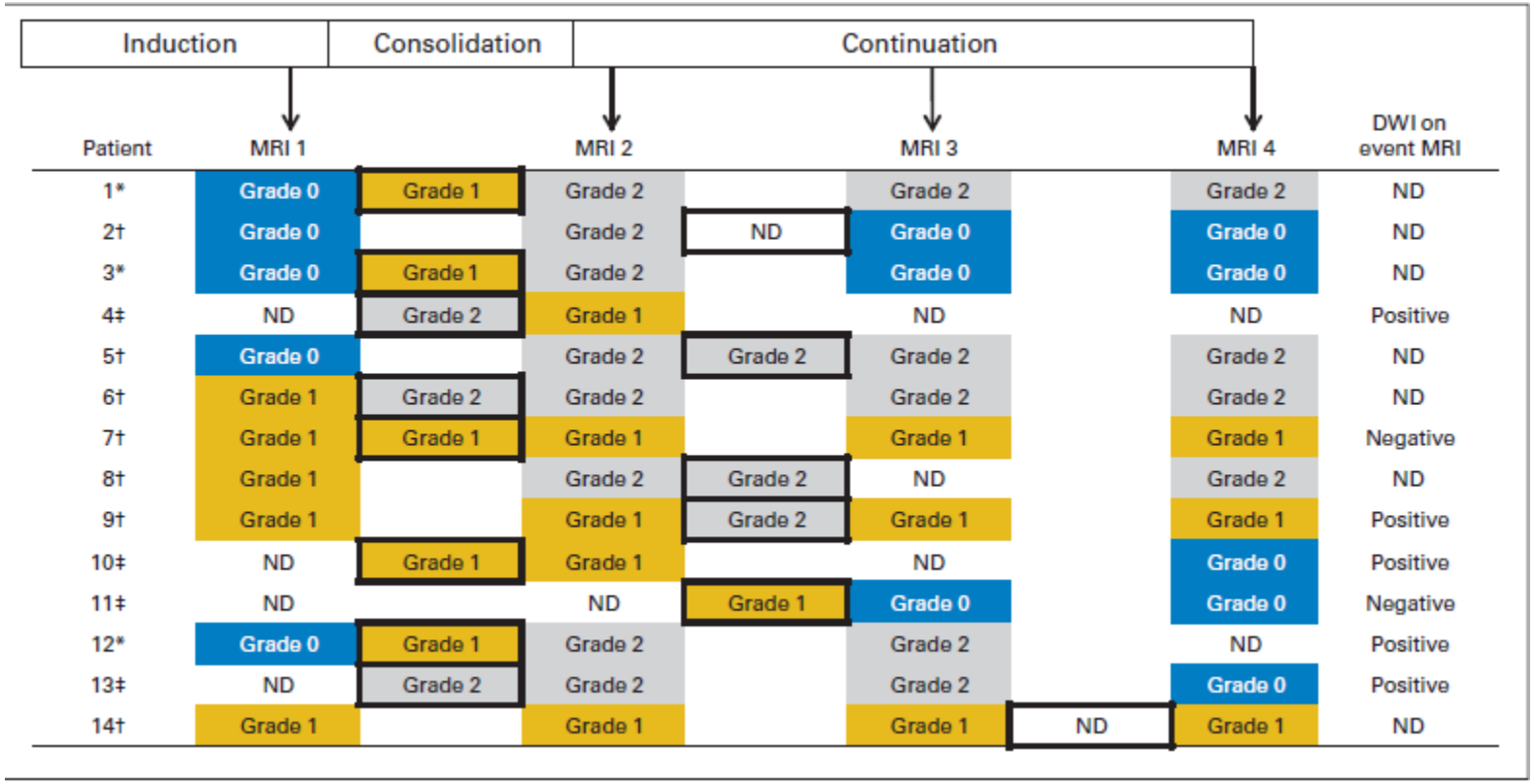

	Induction		Consolidation		Continuation				
Patient	MRI 1		MRI 2		MRI 3		MRI 4		DWI on event MRI
1*	Grade 0	Grade 1	Grade 2		Grade 2		Grade 2		ND
2†	Grade 0		Grade 2	ND	Grade 0		Grade 0		ND
3*	Grade 0	Grade 1	Grade 2		Grade 0		Grade 0		ND
4‡	ND	Grade 2	Grade 1		ND		ND		Positive
5†	Grade 0		Grade 2	Grade 2	Grade 2		Grade 2		ND
6†	Grade 1	Grade 2	Grade 2		Grade 2		Grade 2		ND
7†	Grade 1	Grade 1	Grade 1		Grade 1		Grade 1		Negative
8†	Grade 1		Grade 2	Grade 2	ND		Grade 2		ND
9†	Grade 1		Grade 1	Grade 2	Grade 1		Grade 1		Positive
10‡	ND	Grade 1	Grade 1		ND		Grade 0		Positive
11‡	ND		ND	Grade 1	Grade 0		Grade 0		Negative
12*	Grade 0	Grade 1	Grade 2		Grade 2		ND		Positive
13‡	ND	Grade 2	Grade 2		Grade 2		Grade 0		Positive
14†	Grade 1		Grade 1		Grade 1	ND	Grade 1		ND

- **12 pacientes** con RMN disponible en el momento del evento tenían leucoencefalopatía.
- **Todos** los pacientes sintomáticos presentaron leucoencefalopatía en algún momento durante el tratamiento.
- **10 pacientes** disponían de screening previo con RMN: 7 pacientes leucoencefalopatía previa.
- De los **12 pacientes** con RMN al final del tratamiento, en 7 pacientes persistía la leucoencefalopatía.

Methotrexate-Induced Neurotoxicity and Leukoencephalopathy in Childhood Acute Lymphoblastic Leukemia.

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Table 3. SNPs on Affymetrix Arrays Associated With Leukoencephalopathy and Clinical Neurotoxicity*

SNP ID	Chromosome	Position	Gene	MAF	Risk Allele	OR	95% CI	P
				Leukoencephalopathy				
rs4145201	6	17007422	—	0.33	C	0.42	0.29 to 0.61	5.14E−06
rs556269	1	164839754	*FMO9P*†	0.41	T	2.31	1.60 to 3.34	7.79E−06
rs32571	5	14227106	*TRIO*	0.48	C	0.43	0.29 to 0.63	1.73E−05
rs7590550	2	202266660	*MPP4*	0.16	G	2.65	1.69 to 4.15	2.28E−05
rs245311	5	127194498	*LOC728586*	0.29	T	2.72	1.70 to 4.35	2.88E−05
rs10842702	12	26331326	*SSPN*	0.35	C	0.44	0.30 to 0.65	3.03E−05
rs33005	5	14259537	*TRIO*	0.49	G	0.45	0.30 to 0.65	3.20E−05
rs9545873	13	81288492	—	0.42	T	2.09	1.47 to 2.97	3.75E−05
rs1904006	10	53479033	*PRKG1*	0.17	C	0.37	0.23 to 0.60	4.03E−05
rs6632675	X	13245592	—	0.18	C	0.48	0.34 to 0.68	4.08E−05
rs2065920	1	164869647	*FMO9P*†	0.36	C	0.48	0.34 to 0.69	4.46E−05
rs5762295	22	26373959	—	0.03	G	8.11	2.97 to 22.2	4.52E−05
rs1465614	2	16516774	—	0.24	C	0.42	0.28 to 0.64	4.90E−05
rs16985255	22	26371883	—	0.03	G	7.00	2.73 to 17.9	5.03E−05
rs1448686	8	137104691	—	0.41	A	0.47	0.32 to 0.68	5.66E−05
rs17584752	4	108120536	*DKK2*	0.19	C	0.42	0.28 to 0.64	5.71E−05
rs11986485	8	41659544	*ANK1*	0.29	C	0.38	0.24 to 0.61	6.55E−05
rs13267761	8	138930469	*FLJ45872*	0.27	C	0.46	0.31 to 0.67	6.83E−05
rs9466410	6	22722709	—	0.25	C	0.35	0.20 to 0.58	7.17E−05
rs6840582	4	122669925	*LOC729112*	0.28	G	2.59	1.62 to 4.15	7.27E−05
rs7320755	13	109829093	*COL4A2*	0.32	C	0.45	0.31 to 0.67	7.49E−05
rs6841032	4	122670192	*LOC729112*	0.29	G	2.59	1.61 to 4.16	7.97E−05
rs9936750	16	53729375	—	0.18	G	2.48	1.58 to 3.90	8.13E−05
rs11185944	10	91731927	*LOC119358*	0.35	G	2.06	1.44 to 2.96	8.51E−05
rs1034893	17	9013280	*NTN1*	0.17	A	0.27	0.14 to 0.52	8.92E−05
rs17133261	5	100579903	—	0.07	T	3.71	1.92 to 7.18	9.80E−05
				Clinical Neurotoxicity				
rs12379211	9	119127189	*ASTN2*	0.08	C	0.11	0.04 to 0.32	3.65E−05
rs226945	6	3662178	—	0.09	T	11.7	3.57 to 38.2	4.79E−05
rs17626001	14	42139233	—	0.07	C	0.09	0.03 to 0.28	5.17E−05
rs226962	6	3669960	*PXDC1*	0.09	A	0.07	0.02 to 0.25	5.32E−05
rs682518	6	150770134	*IYD*	0.08	G	7.66	2.81 to 20.9	6.84E−05
rs665670	6	150775949	—	0.14	T	9.17	3.03 to 27.7	8.70E−05
rs7887242	X	20931587	—	0.18	T	4.33	2.08 to 9.03	9.13E−05
rs10846690	12	123652370	—	0.13	T	9.84	3.13 to 31.0	9.28E−05
rs10886214	10	85117719	—	0.21	T	8.43	2.89 to 24.6	9.64E−05

Abbreviations: MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.
*$P < .0001$.
†Pseudogene.

Dr. Dapena

High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia.
Skärby TVCh et al. Leukemia (2006) 20, 1955-1962

NOPHO 92 ALL PROTOCOL

- SR: 8 cursos de MTXHD:5 g/m²
- IR: 9 cursos de MTXHD:5 g/m²
- HR: 4 cursos de MTXHD:8 g/m²
- VHR: 2 cursos de MTXHD:8 g/m²

Rescate con LV: (inicio a las 36 horas)

- **MTXHD 5 g/m²**: LV 15 mg/m² y, a las 42 horas: LV 15 mg/m² (ajustes en función de tabla) y, posteriormente cada 6 horas hasta niveles < 0.2 µM.

- **MTXHD 8 g/m²**: LV 50 mg/m² y, a las 39 y 42 horas: LV 15 mg/m² (ajustes en función de tabla) y, posteriormente cada 6 horas hasta niveles < 0.2 µM.

VHR groups and relapse

	Relapse, yes/no	S-MTX$_{23}$ (µM), course 1	S-MTX$_{23}$ (µM), median over courses	LV dose (mg/m^2), course 1	LV dose (mg/m^2), median over courses
SR	Yes ($n=25$)	81.0 (62.0–104.2)	72.0 (64.7–84.5)	107.9 (75.0–195.0)	91.0 (88.2–138.1)
	No ($n=127$)	96.5 (80.0–126.6)	84.0 (72.5–96.8)	91.2 (82.0–169.2)	93.9 (87.5–116.8)
IR	Yes ($n=33$)	74.8 (63.3–88.4)	82.0 (68.5–88.4)	167.7 (91.7–255.0)	116.9 (91.6–201.2)
	No ($n=138$)	74.0 (61.3–98.0)	75.4 (62.9–90.0)	105.0 (88.0–169.8)	93.8 (85.7–112.4)
HR	Yes ($n=20$)	146.2 (120.0–195.0)	148.9 (128.8–168.5)	387.6 (269.9–605.0)	297.8 (243.9–492.5)
	No ($n=53$)	136.0 (108.2–180.0)	128.0 (112.3–151.5)	253.8 (156.9–440.1)	213.0 (159.0–306.0)
VHR	Yes ($n=16$)	146.6 (122.0–193.0)	134.4 (115.8–183.9)	264.4 (158.5–380.0)	233.8 (194.7–481.5)
	No ($n=33$)	144.5 (119.0–170.0)	149.5 (119.0–167.9)	281.3 (181.9–412.8)	324.0 (206.4–469.4)
All	Yes ($n=94$)	97.5 (72.3–138.0)	89.7 (75.0–130.0)	202.3 (107.1–384.6)	189.8 (91.7–282.3)
	No ($n=351$)	95.4 (72.0–129.0)	86.2 (70.0–117.5)	120.0 (89.3–243.6)	105.0 (90.0–175.9)

Table 1 Distribution of patients in the SR, IR, HR and VHR groups in the cohort, background material and case–controls

	All NOPHO (n = 1018)	*Cohort (DK-N-S) (n = 419)*	*Case–controls (Finland) (n = 26)*
Sex (male/female)	547/471 (54/46%)	238/181 (57/43%)	13/13 (50/50)
Age (years); median at diagnosis (p25–p75)	4 (2–8)	4 (3–7)	3 (2–6)
WBC at diagnosis (p25–p75)	9.7 (4–33.6)	9.4 (3.9–32)	10.1 (6.3–21.9)
Immunphenotype (T/precursor-B)	100/896 (10/90%)	44/370 (11/89%)	0/25 (0/100%)
Number of relapses	196 (19%)	85 (20%)	9 (35%)
Risk group: (SR/IR//HR/VHR)	332/371/200/115 (33/36/20/11%)	146/157/70/46 (35/37/17/11%)	6/14/3/3 (23/54/12/12%)

Abbreviations: HR, high risk; IR, intermediate risk; NOPHO, Nordic Society of Paediatric Haematology and Oncology; SR, standard risk; VHR, very high risk; WBC, white blood cells.

Dr. Dapena

How Long Can Folinic Acid Rescue Be Delayed After High-Dose Methotrexate Without Toxicity? Cohen I et al. Pediatr Blood Cancer 2014;61:7-10

To determine the optimal time of folinic acid rescue after methotrexate (MTX) treatment in patients with ALL, we selected and evaluated relevant studies that included doses, rescue delay, and side effects. Rescue at 42–48 hours resulted in considerable toxicity, except when low doses of MTX were used (1 g/m2) or serum MTX levels remained consistently low at 24, 30, and 36 hours. Rescue started at 30–36 hours was safe. In the absence of evidence that later rescue improves prognosis, we suggest that folinic acid rescue (105 mg/m2) **be started no later than 36 hours from the start of MTX (5–6 g/m2**).

However, since 36-hour rescue has proven safe, and there is no evidence that later rescue improves prognosis, we suggest that it may be safer, easier, and more cost-effective to rescue all patients at 36 hours. The neurotoxicity recently described after lower-dose folinic acid should be taken into account when future dose schedules are designed. Any study that continues to use lower dose folinic acid should at least closely follow patients to access neuropsychological damage.

The Correlation Between Dose of Folinic Acid and Neurotoxicity in Children and Adolescents Treated for Osteosarcoma With High-dose Methotrexate (HDMTX): A Neuropsychological and Psychosocial Study.

Background: This study has been performed to examine the currently used doses of folinic acid (FA) and to determine the importance of the dose of FA in preventing subtle neurotoxicity. Thirty osteosarcoma patients were an appropriate population studied as they have no intrinsic neurological involvement. The neuropsychological and psychosocial status was tested in 2 groups of patients treated with similar protocols containing repeated doses of high-dose methotrexate, but different doses of FA. The patients received 300 to 600 mg/m^2 or 120 to 250 mg/m^2 FA in their protocols.
Methods: Eighteen tests or subtests of neuropsychological assessment were tested.
Results: Eleven of 18 tests were significant at the *P*=0.025 level favoring the group treated with high dose of FA. There were no clear results in the psychosocial measures with only a single measure of self-esteem (understanding) being significantly higher (*P*=0.024) in the group treated with high dose of FA, other measures had no statistical significance.
Conclusions: A correlation between a higher dose of FA after high-dose methotrexate and a better neuropsychological status was clearly shown. The doses of FA used in the low FA group, 120 to 250 mg/m^2, were similar to those used by several groups treating children with leukemia; some have used even lower doses and report gross neurotoxicity.

Dr. Dapena

Challenging the clinical relevance of folinic acid over rescue after high dose methotrexate (HDMTX). Cohen Ian. Medical Hypotheses 81 (2013) 942-947

A b s t r a c t

The hypothesis: The use of adequate folinic acid rescue (in clinically relevant doses) after high dose methotrexate will prevent neurotoxicity without reducing treatment results.
Methods: A literature search was performed to test the hypothesis that no evidence for the existence of folinic acid over-rescue of high-dose methotrexate (MTX) in clinically relevant situations exists (evidence that too much folinic acid reduced cure rate).
Empirical data: Examples of folinic acid over-rescue after lower doses of MTX were found and has been cited as evidence of over rescue of high dose MTX. Mega doses of folinic acid, used when toxic levels of MTX occurred, also could neutralize the MTX effect. Data were found to support the contention that higher levels of MTX require disproportionally higher folinic acid doses for rescue. Careful examination of the available studies after HDMTX yielded more convincing alternative explanations for reduction in cure rate than over rescue. Little convincing evidence for the existence of over rescue after HDMTX was found.
Discussion: The rescue of high-dose MTX with an appropriate dose of folinic acid that can prevent toxicity, especially neurotoxicity, was not shown to reduce the therapeutic effect. No evidence was found that higher doses of folinic acid after high dose MTX reduces the therapeutic effect.
Consequences of the hypothesis: Acceptance of the hypothesis can prevent harm being caused (especially brain damage) by reversing the trend of dose reduction in FA rescue. The recognition that the use of higher folinic acid doses is safe, can prevent neurotoxicity, and does not reduce prognosis has important implications for the development of effective non toxic treatment protocols.

Defining the appropriate dosage of folinic acid after high-dose methotrexate for childhood acute lymphatic leukemia that will prevent neurotoxicity without rescuing malignant cells in the central nervous system. Cohen I. J Pediatr Hematol Oncol. 2004 Mar;26(3):156-63

Dr. Dapena

High leucovorin doses during high-dose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. Skärby TVCh et al. Leukemia (2006) 20, 1955-1962

NOPHO 92 ALL PROTOCOL

- Los resultados sugieren que las dosis altas de LV durante el MTXHD aumentan el riesgo de recaída en los niños tratados por LLA según el Protocolo NOPHO 92 ALL
- La influencia negativa de los niveles altos de LV en la recaída parece superar los supuestos efectos beneficiosos de las altas concentraciones de MTX.

Table 4 Univariate Cox and conditional logistic regression analyses with 2 log MTX_{23} and 2 log LV dose value from the first course and the median of all courses as covariates

	SR		*IR*		*HR*		*VHR*		*All*	
Factor	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P
2log LV, first course	1.19 (0.87–1.63)	0.28	1.22 (0.99–1.50)	0.059	1.37 (0.93–2.02)	0.11	0.94 (0.59–1.52)	0.83	1.20 (1.02–1.39)	**0.020**
2log MTX_{23}, first course	0.54 (0.36–0.81	**0.003**	1.10 (0.51–2.36)	0.81	1.43 (0.67–3.08)	0.36	2.35 (0.52–10.66)	0.27	0.87 (0.61–1.26)	0.47
2log LV, median over courses	1.29 (0.51–3.24)	0.59	1.20 (0.94–1.53)	0.15	2.80 (1.30–6.01)	**0.008**	0.93 (0.54–1.61)	0.80	1.22 (1.01–1.49)	**0.037**
2log MTX_{23}, median over courses	0.26 (0.13–0.53)	**<0.001**	2.04 (0.78–5.31)	0.14	3.36 (1.06–10.59)	**0.039**	1.08 (0.23–5.16)	0.92	1.07 (0.63–1.80)	0.81

Abbreviations: CI, confidence interval; HR, high risk; IR, intermediate risk; LV, leucovorin; MTX_{23}, serum methotrexate concentration 23 h after start of methotrexate administration; RR, relative risk for doubling the LV dose or the MTX_{23} concentration in the SR, IR, HR and VHR groups; SR, standard risk; VHR, very high risk.
Bold values indicate $P<0.05$

Table 5 Multivariate Cox and conditional logistic regression analyses with the two factors 2 log LV and 2 log MTX_{23} as covariates using data from the first course and the median over courses, respectively

		SR		*IR*		*HR*		*VHR*		*All*	
Analysis	*Factor*	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P	*RR (95% CI)*	P
First course	2 log LV	1.27 (0.88–1.83)	0.19	1.27 (1.01–1.60)	**0.044**	1.23 (0.78–1.94)	0.37	0.86 (0.52–1.40)	0.53	1.22 (1.03–1.44)	**0.022**
	2 log MTX_{23}	0.49 (0.31–0.78)	**0.003**	0.69 (0.27–1.74)	0.433	1.06 (0.44–2.53)	0.90	4.38 (0.78–24.63)	0.093	0.72 (0.48–1.09)	0.12
Median over courses	2 log LV	1.40 (0.54–3.62)	0.49	1.15 (0.88–1.50)	0.32	2.62 (1.16–5.92)	**0.02**	0.88 (0.50–1.54)	0.65	1.24 (1.02–1.52)	**0.035**
	2 log MTX_{23}	0.28 (0.13–0.59)	**0.001**	1.67 (0.50–5.56)	0.40	2.82 (0.60–13.36)	**0.19**	2.02 (0.35–11.61)	0.43	0.91 (0.50–1.67)	0.77

Abbreviations: CI, confidence interval; HR, high risk; IR, intermediate risk; LV, leucovorin; MTX_{23}, serum methotrexate concentration 23 h after start of methotrexate administration; RR, relative risk for doubling the LV dose or the MTX_{23} concentration in the SR, IR, HR and VHR groups; SR, standard risk; VHR, very high risk.
Bold values indicate $P<0.05$.

Dr. Dapena

HDMTX en tumores sólidos y hematológicos: Rescate.

Dra. M. Dolores Aumente.

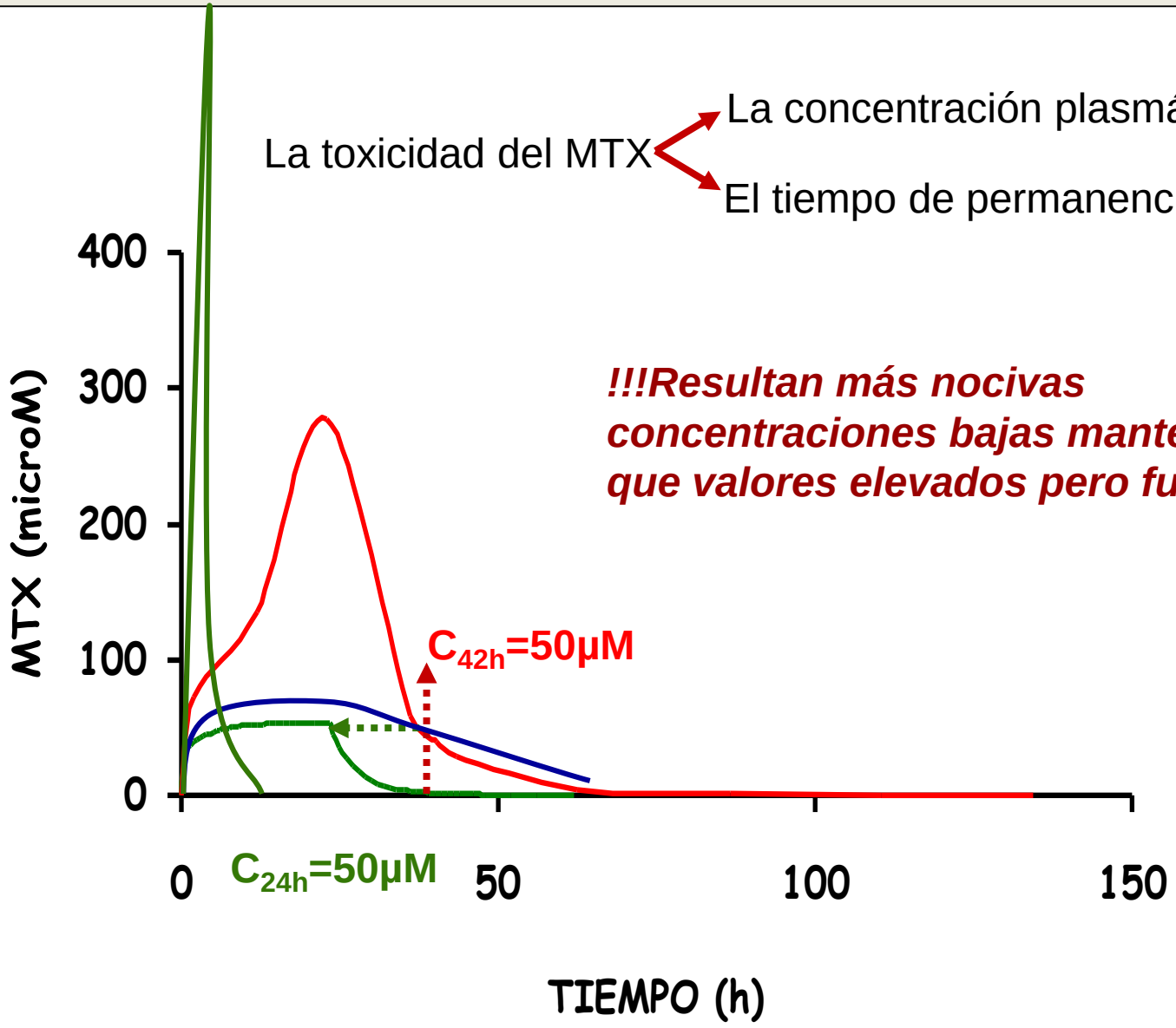
- **Concentraciones críticas de MTX.**

- **¿Cuál es el mejor esquema de incremento de la dosis de ác. folínico?**

- **Estrategia de monitorización de TDM para reducir las intoxicaciones por MTX**

¿Cuáles son las concentraciones críticas que me alertan de la necesidad de incrementar el rescate?

La toxicidad del MTX
- La concentración plasmática alcanzada
- El tiempo de permanencia en el organismo,



!!!Resultan más nocivas concentraciones bajas mantenidas en el tiempo que valores elevados pero fugaces!!!

Dra. Aumente

¿Cuáles son las concentraciones críticas que me alertan de la necesidad de incrementar el rescate?

MTX en infusión de 24 horas

Régimen (protocolo)	Tiempo desde inicio infusión MTX	[MTX] con eliminación normal
2.5-5g/m^2 en 24 horas (ALL-Total Therapy XV, St jude)	23h	<150µM
	42h	≤1µM
	66h	≤0.2µM
5g/m^2 en 24 horas (ALL-BFM 2000) ((NHL-BFM 95)	24h	<150µM
	36h	<3µM
	42h	≤1µM
	48h	≤0.4µM
1g/m^2 en 24 horas* (NHL-BFM 95)	24h	<30µM
	36h	<1µM
	48h	<0.25µM

*Los valores indicados para la terapia de 1g/m^2 en 24 horas se basan en los datos de Zintl y Sauerbrey, Jena y se han sugerido en el protocolo NHL-BFM95.

La [MTX] asociada con toxicidad: **C_{42h}>1 µM**

¡¡¡Si el rescate adecuado se retrasa mas de 42h la citotoxicidad del MTX puede ser irreversible!!!!

Dra. Aumente

MTX en infusión de 4 horas

Régimen (protocolo)	Tiempo desde inicio infusión MTX	[MTX] con eliminación normal
8g/m^2 en 4 horas (Nirenberg et al. 1977)	24h	<10
	48h	<1
	72h	<0.1
5g/m^2 en 4 horas (NHL-BFM 95)	4h	<1000µM
	24h	<8µM
	36h	<2µM
	42h	<1µM
	48h	<0.25µM
1g/m^2 en 4 horas* (NHL-BFM 95)	4h	<200µM
	24h	<2µM
	36h	<1µM
	42 h	<0.4µM
	48h	<0.25µM

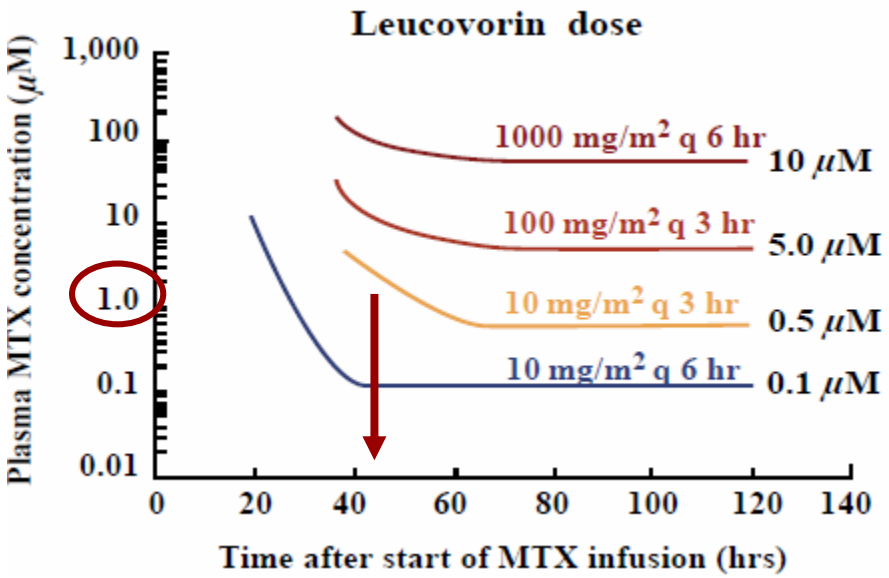
Estos valores se han deducido de lo indicado por Sasaki et al. (1985) y se han sugerido en el protocolo NHL-BFM 95, pero si al dosis es de 3g/m^2 habría que adaptar los niveles de modo que el criterio sería $[MTX]_{24h}<5$.

La [MTX] asociada con toxicidad: **C_{24h}>10 µM**

Dra. Aumente

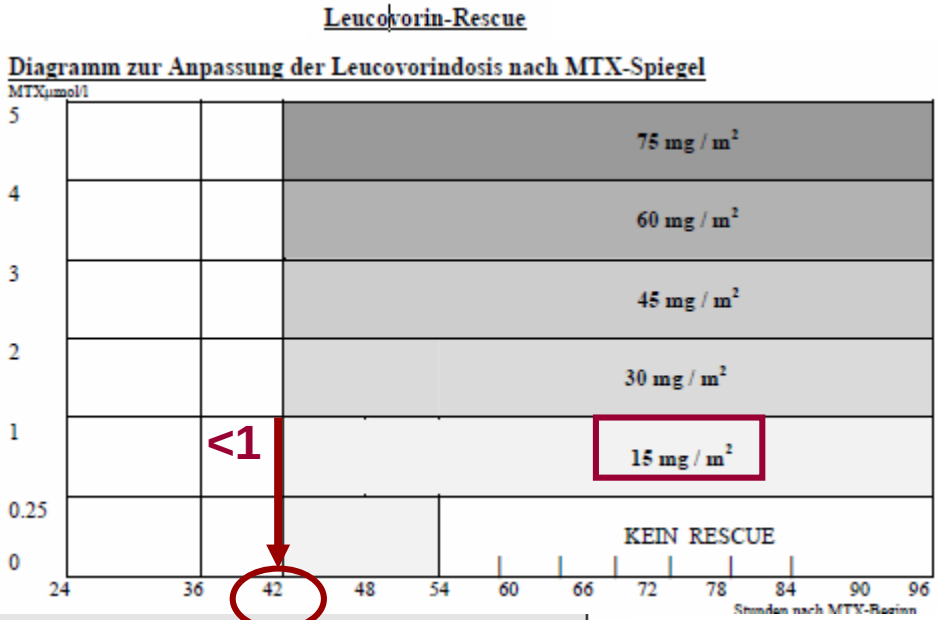
¿Cuál es el mejor esquema de incremento de la dosis de Ac folínico?

Diagrama de Bleyer (1989)



BFM group

15mg/m² (3 dosis) 42,48,54h (stop <0.25μM)



St. Jude Children's Research Hospital

15mg/m² (5 dosis) 42,48,54,60,66h (stop <0.1μMl)

Consolidation Therapy

Time from start of MTX Concentration	Plasma concentration thresholds for action	Recommended Leucovorin rescue
42 hr	< 1 μM	protocol rescue (10 mg/m² po q 6 hrs x 5 doses for LR and 15 mg/m² IV/po x 5 doses for SR/HR)
	1-2 μM	30 mg/m² po/IV q 6 hrs
	2-5 μM	50 mg/m² IV q 6 hrs
	5-10 μM	100 mg/m² IV q 6 hrs
	10-20 μM	200 mg/m² IV q 6 hrs
	>20	Individualized

Dra. Aumente

¿Cuál es el mejor esquema de incremento de la dosis de Ac folínico?

Con los niveles extraídos a 2, 12, 23 y 36 horas y un algoritmo Bayesiano se predice la $[MTX]_{42h,}$.
Corregir la dosis de LV según la siguiente tabla de dosificación[6,7,8]. Y extraer una muestra a las 42h.

$[MTX]_{42h}$	Dosis de LV	
<1µM	15mg/m^2/6h IV	
1-2µM	30mg/m^2/6h IV	
2-3µM	45mg/m^2/6h IV	
3-4µM	60mg/m^2/6h IV	
4-5µM	75mg/m^2/6h IV	
5-10µM	100mg/m^2/6h IV	o Dosis LV(mg/24h)=[MTXµM]xPeso (kg) en infusión continua o repartido en 4 tomas
10-20µM	200mg/m^2/6h IV	
20-50µM	500mg/m^2/6h IV	
>50µM	500mg/m^2/3h IV	
-Si la dosis de LV es > 20mg/kg o > 100mg/m^2 aumentar el tiempo de infusión a 1h (1g de LV contiene 4mEq de calcio).		

Con el nivel las 42 horas: corregir rescate y extraer nueva muestra a las 60h

Si $[MTX]_{42h\ real}$ = $[MTX]_{42h\ predicha}$	Reafirmar la dosis de LV pautada.
Si $[MTX]_{42h\ real}$ > $[MTX]_{42h\ predicha}$	Administrar inmediatamente una dosis suplementaria de LV que complete la dosis que le hubiera correspondido, sin esperar a las 48h y continuar con la dosis corregida.
Si $[MTX]_{42h\ real}$ < $[MTX]_{42h\ predicha}$	Reajustar la dosis de LV
Si $[MTX]_{42h\ real}$ <0.2µM	Continuar con 15mg/m^2/6h IV hasta las 54h (última dosis)

Dra. Aumente

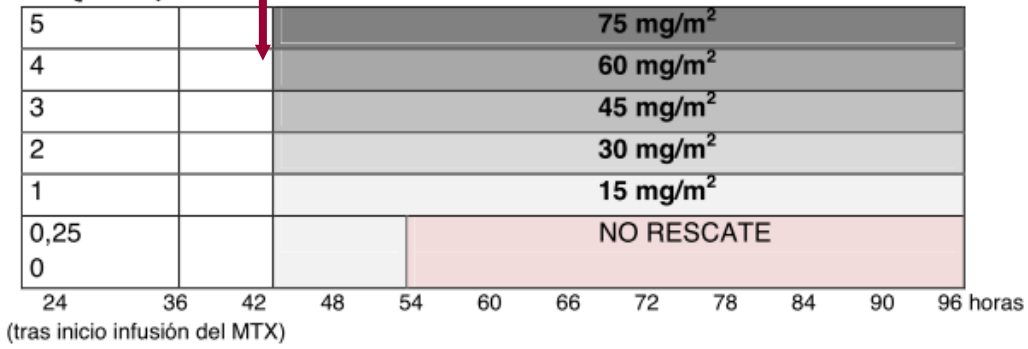
¿Cuál es la mejor estrategia para la monitorización de MTX?

LAL/SEHOP-PETHEMA 2013

(para niños mayores de 1 año y ≤ 19 años)

Tiempo desde inicio infusión de MTX (+ horas)	Nivel de MTX (µmol/l)	Dosis de Leucovorin ev (mg/m^2)
24	≤ 150,0	-
36	≤ 3,0	-
42	≤ 1,0	15
48	≤ 0,4	15
54	≤ 0,4	15

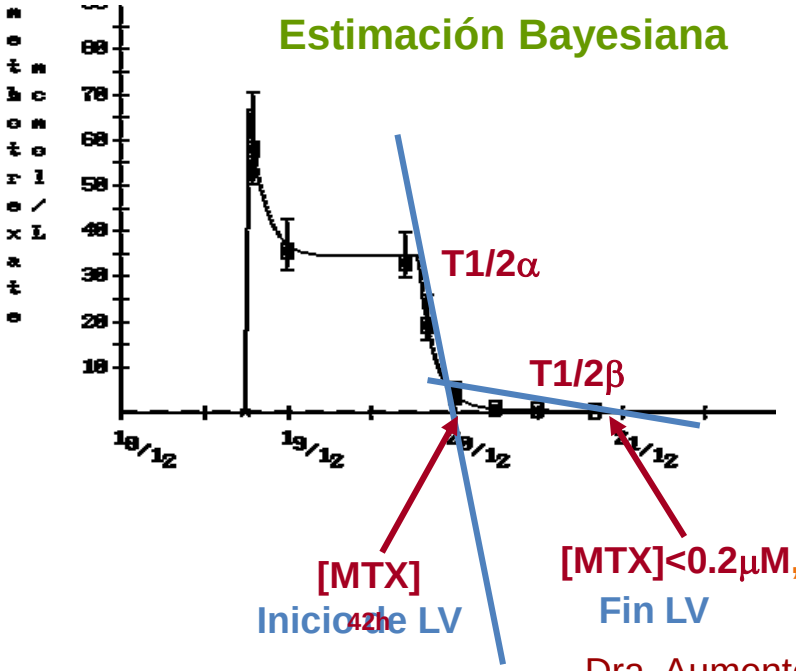
Tabla 16.2.: Dosificación de Leucovorin en relación con niveles de MTX



Leucovorin [mg] = concentración plasmática MTX [µmol/l] x peso corporal [kg]

T1/2α >3.5h

Estimación Bayesiana

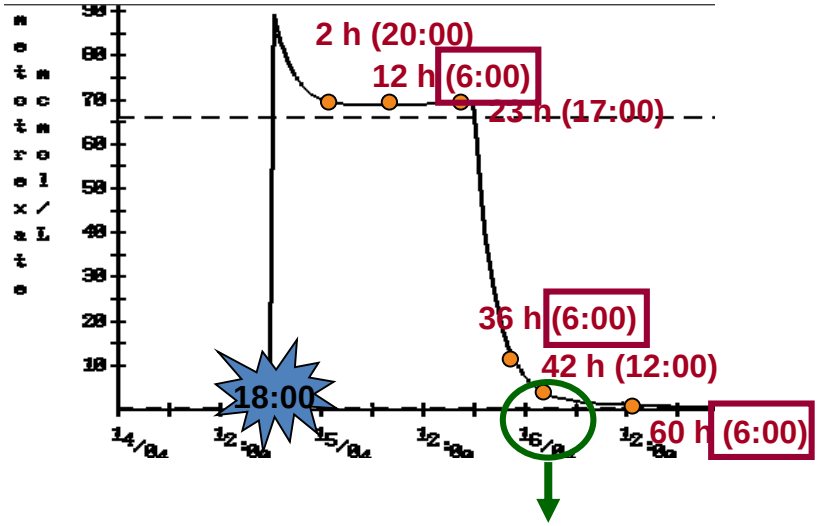


Dra. Aumente

Protocolo TDM

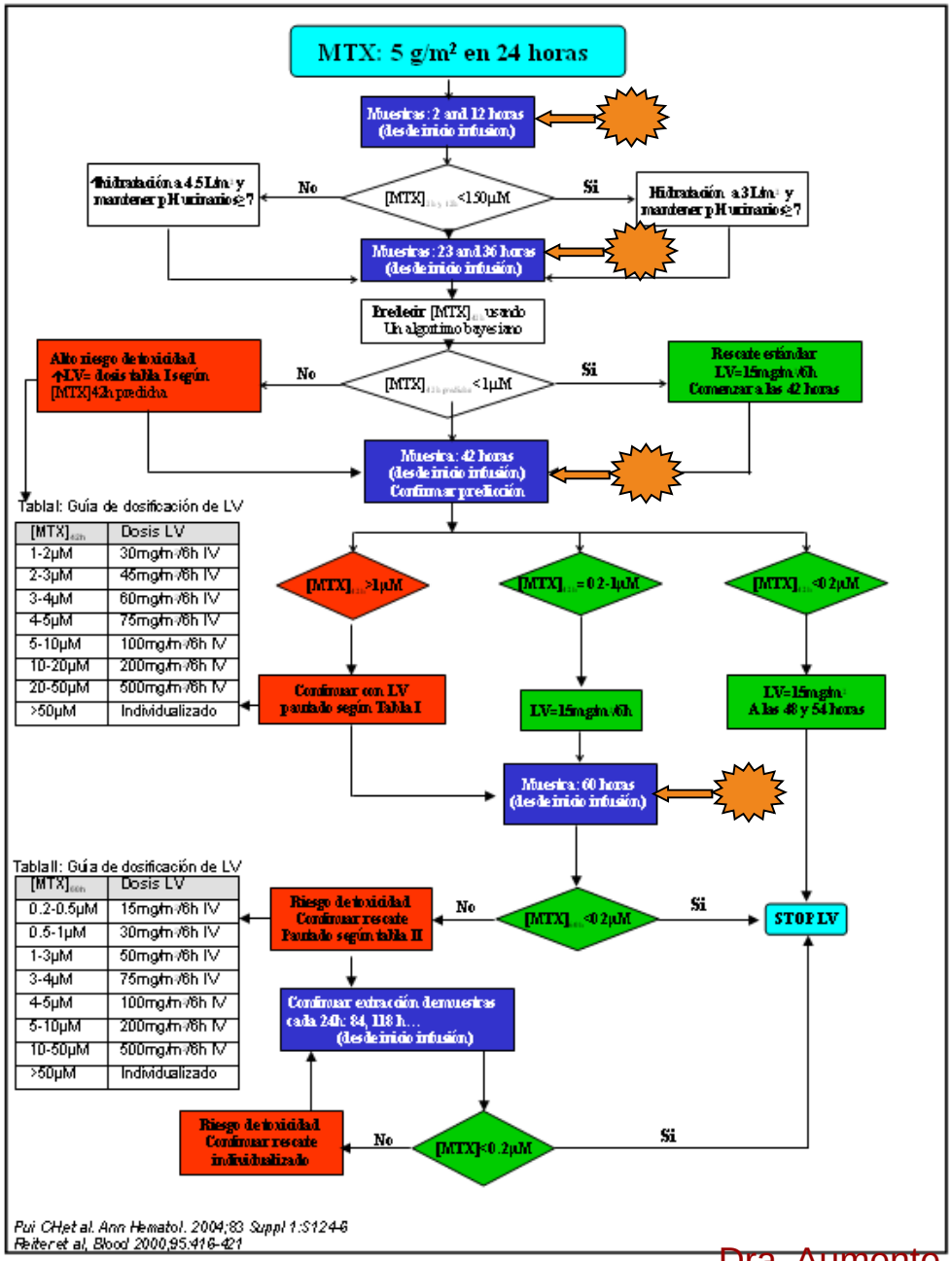
MTX en 24 horas

Extracción de muestras:
2, 12, 23, 36, 42, 61 horas



Predicción de C_{42h}

Corregir rescate con LV



Pui CH et al. Ann Hematol. 2004;83 Suppl 1:S124-6
Reiter et al, Blood 2000;95:416-421

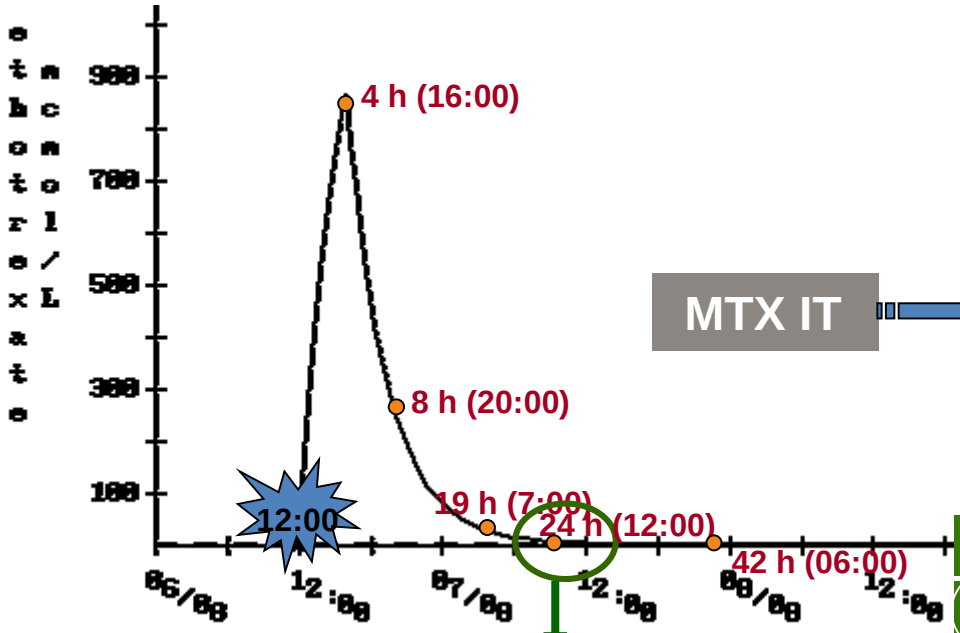
Dra. Aumente

MTX en 4 horas

Extracción de muestras:
4 , 8, 18, 24, 44 horas

MTX: 2.04g (3g/m^2 en 4h) COPAMD

3 años/Linfoma Burkitt abdominal - IIA



MTX IT

Horas	[MTX]µM			
	Ciclo1	Ciclo2	Ciclo3	Ciclo4
4 h	205.6	184.8	240.4	352.4
8 h	35.6	16.8	44	64.8
19 h	1.16	0.66	1.09	1.86
24 h	3.42	1.37	0.97	2.58
43 h	0.16	0.12	0.1	0.109
66 h		0.04		

Predicción de C_{24h}

Corregir rescate con LV

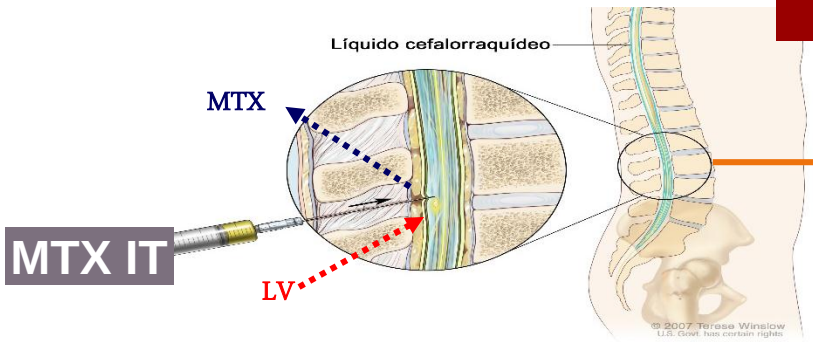
Rescate

24h	30h	36h	42h	46h	48h
LV (mg/m^2)					
15	-	-	-	30	15….

Dra. Aumente

¿Cuándo se debe administrar el MTX por vía intratecal?

Nunca administrar el MTX intratecal durante el rescate con LV

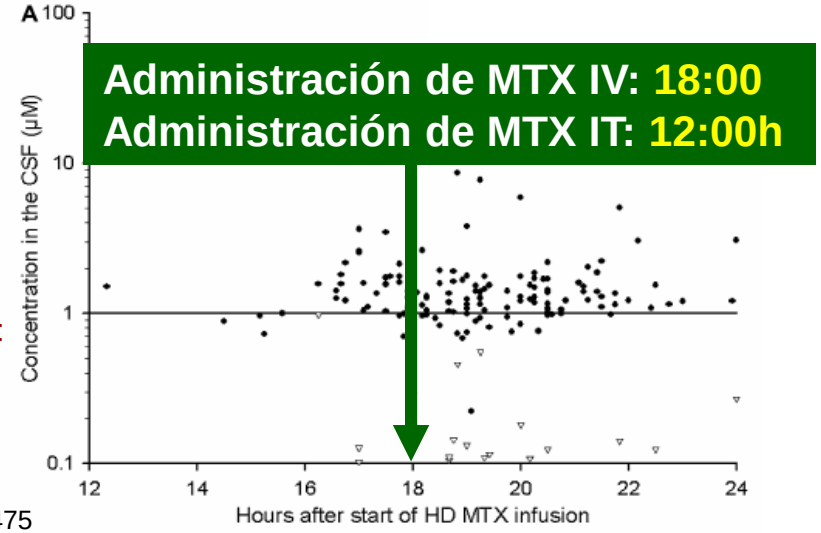


Cociente LCR : plasma

LV= 3-4: 1

Kamen BA, et al. J Pediatric Hematol Oncol 2004; 26(6):333-5

El MTX IT se debe administrar durante la infusión del MTX sistémico



Protocols of the BFM group:

MTX=5 g/m^2 en 24 h

Niemann A et al. Ther Drug Monit 2010: 32:467-475

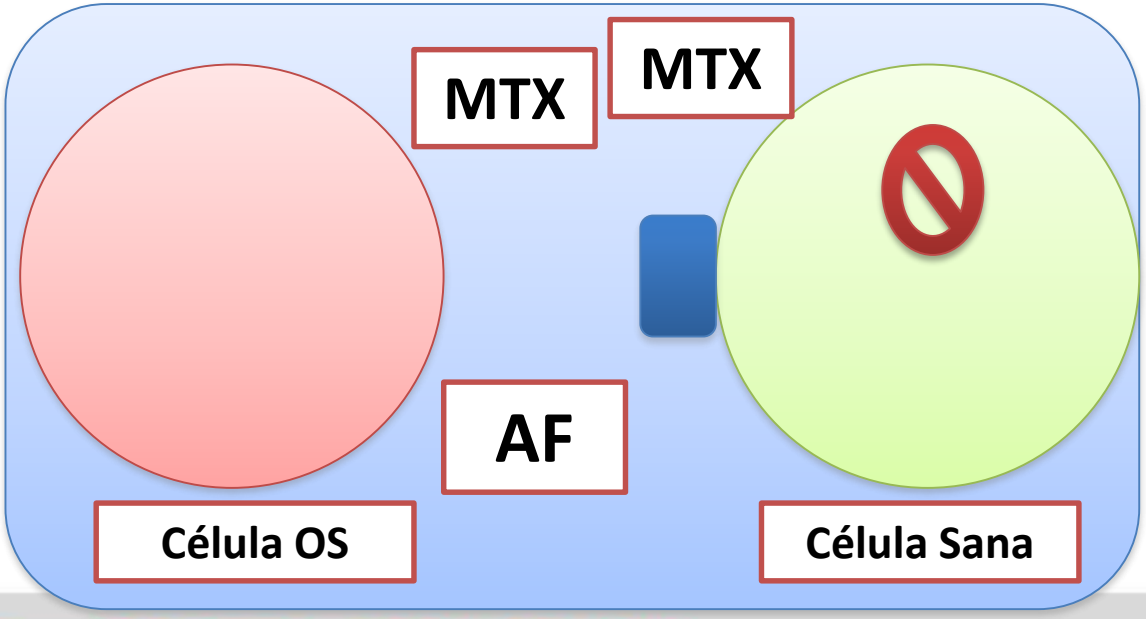
Dra. Aumente

HDMTX en tumores sólidos y hematológicos: Rescate.

Dr. Francisco José Bautista.

- **Riesgos y beneficios de una dosis excesiva vs insuficiente de ácido folínico a corto y largo plazo en los tumores sólidos.**

¿Un rescate excesivo tiene trascendencia en cuanto a la eficacia del MTX sobre las células malignas en el osteosarcoma?



¿Un rescate excesivo tiene trascendencia en cuanto a la eficacia del MTX sobre las células malignas en el osteosarcoma?

Dr. Bautista

Challenging the clinical relevance of folinic acid over rescue after high dose methotrexate (HDMTX) ☆

Ian J. Cohen *

1) The effect of methotrexate pharmokinetics and of leucovorin rescue on the prognosis of osteosarcoma. Graf N. Klinische Padiatrie 1990.

- 19 pacientes OS. MTX-HD (12g/m^2). Niveles MTX fin infusión >1300: Mejor OS
- 27% de los pacientes que requirieron dosis altas de AF recayeron Vs 9%
- Análisis multivariante: Dosis altas de AF se relacionan con peor OS

2) High-dose methotrexate pharmacokinetics and outcome of children and young adults with osteosarcoma. Crews KR. Cancer 2004.

- 140 pacientes OS. MTX-HD (12g/m^2). Niveles MTX fin infusión >1500: Peor OS
- "Dosis altas de AF por niveles altos de MTX haya podido comprometer la eficacia del MTX en estos pacientes"

¿Deben ser iguales las dosis de rescate con ácido folínico en niños y adultos?

Dr. Bautista

-Las dosis de AF recomendadas en los protocolos OS para niños y adultos con MTX 12g/m^2 son de 12-15mg/m^2/dosis cada 6 horas a partir de H20-H28 según los protocolos.

-Sólo de forma individualizada, en pacientes adultos expuestos a dosis altas de MTX, el rescate con AF podría aumentarse (o adelantarse) para evitar la toxicidad.

¿Un rescate bajo con ácido folínico puede incrementar el riesgo de neurotoxicidad?
¿Neurotoxicidad tardía y MTX?

Dr. Bautista

Ann Neurol. 1989 Apr;25(4):365-72.

High-dose leucovorin reverses acute high-dose methotrexate neurotoxicity in the rat.

Phillips PC[1], Thaler HT, Allen JC, Rottenberg DA.

Modelos animales murinos expuestos a dosis altas de MTX
La utilización de ácido folínico a dosis altas Vs dosis bajas permitió:
-Reducir el metabolismo de la glucosa a nivel cerebral
-Mejorar el comportamiento y disminuir la actividad EEG anormal

The Correlation Between Dose of Folinic Acid and Neurotoxicity in Children and Adolescents Treated for Osteosarcoma With High-dose Methotrexate (HDMTX): A Neuropsychological and Psychosocial Study

Esther Bonda-Shkedi, MSc,† Myriam Weyl Ben Arush, MD,‡ Chaim Kaplinsky, MD,§‖ Shifra Ash, MD,*‖ Yaakov Goshen, MD,*‖ Isaac Yaniv, MD,*‖ and Ian J. Cohen, MB, ChB*‖*

¿Un rescate bajo con folinato cálcico puede incrementar el riesgo de neurotoxicidad? ¿Neurotoxicidad tardía y MTX?

Dr. Bautista

Sequelae of osteosarcoma medical therapy: a review of rare acute toxicities and late effects

Katherine A Janeway, Holcombe E Grier

- Neurotoxicidad aguda: 0,4-5% de los pacientes
- Muy variable: Trastornos comportamiento, ceguera cortical, convulsiones…aunque en general asociada a un buen pronóstico
- No relacionado con altas concentración de MTX o eliminación retardada
- Recurrencia inusual

Transient Neurologic Disturbances Induced by High-Dose Methotrexate Treatment

NORMAN JAFFE, MD, YOICHI TAKAUE, MD, TAKASHI ANZAI, MD, AND RESA ROBERTSON, RN, PNP

HDMTX en tumores sólidos y hematológicos: Rescate.

Dra. Azucena Aldaz.

- **Tiempo óptimo de inicio y finalización de rescate con ácido folínico en OS.**
- **Dosis óptima de rescate con ácido folínico.**
- **Concentraciones/tº críticas y cambios en el rescate.**

EURAMOS-1

Time after starting MTX	MTX plasma concentration (umol/L)					
	<0.2	0.2-0.7	0.71-2	2.1-19.9	20-100	**>100**
24hrs	None	15mg/m² 6 Hourly	15mg/m² 6 Hourly	15mg/m² 6 Hourly	60mg/m² 6 Hourly	**Inform consultant**
48hrs	None	15mg/m² 6 Hourly	15mg/m² 6 Hourly	150mg/m² 6 Hourly	300mg/m² 3 Hourly	**Inform consultant**
72hrs	None	30mg/m² 6 Hourly	150mg/m² 6 Hourly	750mg/m² 3 Hourly	3000mg/m² 3 Hourly	**Inform consultant**

Guidance for the adjustment of folinic acid dose during delayed methotrexate excretion

Upper limit of serum methotrexate: At 24 hours is 20micromol/L
At 48 hours is 2micromol/L
At 72 hours is 0.2micromol/L

$$\text{Total daily dose of folinic acid}^{*} = \frac{\text{Patient's actual serum methotrexate x standard daily dose of folinic acid}}{\text{Upper limit of serum methotrexate for the actual day and time}}$$

*Higher doses of folinic acid should be given IV every 3 hours

- Ideally MTX should be started early in the morning to allow correct interpretation of levels taken the following day. Folinic acid rescue **MUST** start 24 hours from the start of MTX infusion as prescribed.
- Patients are to have daily blood tests for U&Es as well as MTX levels every 24 hours after the start of MTX infusion until levels are < 0.2 micromol/L.

Dra Aldaz

Practical issues with high dose methotrexate therapy

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Monitoring of plasma MTX level is very important to improve the safety of HDMTX therapy. MTX levels should be followed until the plasma level is less than 0.1 μM. Plasma MTX levels are usually measured at 24, 48 and 72 h after starting the MTX infusion (Gaies et al., 2012).

Gaies, E., Jebabli, N., Trabelsi, S., Salouage, I., Charfi, R., et al, 2012. Methotrexate side effects: review article. J. Drug Metab. Toxicol. 3, 125.

Leucoverin rescue should be started within 24–36 h of the start of the MTX infusion. Dose and frequency of leucoverin depend on the HDMTX protocol used. Commonly used doses of leucoverin are in the range of 10–15 mg/m^2, given every 6 h until plasma MTX levels are less than 0.2 μM (Olsen, 1991).

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Cancer 68:1247–1250, 1991.

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No data could be found concerning high-dose MTX disposition in obese patients, thus the initial dosage of MTX was chosen as 8 g/m^2 with plans to increase to 10 g/m^2 based on patient tolerance (*i.e.*, mucositis, neutropenia). During each dose of MTX, pharmacokinetic monitoring of MTX was performed to optimize the dosage and duration of leucovorin therapy.

Twenty-four hours after the initiation of MTX therapy, intravenous leucovorin rescue was administered at doses adjusted according to MTX serum concentrations. After 24 hours of intravenous leucovorin rescue, oral leucovorin was administered every 6 hours at doses adjusted according to MTX serum concentrations until MTX serum concentrations fell below 0.05 μmol/l.

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Therapeutic Drug Monitoring
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C_{max} at the end of an 8-h infusion. Folinic acid rescue was initiated 36 h after the end of the HDMTX infusion and was continued until the MTX concentration fell below 10^{-7} *M*. The dose of citrovorum factor delivered intravenously every 6 h was calculated from the following formula: folinic acid in mg = 10 × [MTX] in mg/L × 0.76 × weight in kg (16). Hydration and urine alkalinization was begun 12 h before HDMTX infusion and was continued for the total duration of folinic acid rescue. Three liters of 5% glucose solution containing a total of 40 mmol sodium bicarbonate and 20 mmol potassium chloride were administered daily to maintain urine pH ≥7 and urine output ≥200 ml/h. After each miction, urinary pH was determined and additional sodium bicarbonate was given if necessary.

Plasma concentrations were measured after 4 and 5 h to perform Bayesian estimation of the pharmacokinetic parameters. Pharmacokinetic parameters

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Pediatr Blood Cancer 2008;50:1176–1180

The Memorial Sloan Kettering Cancer Center Experience With Outpatient Administration of High Dose Methotrexate With Leucovorin Rescue

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Richard Gorlick, MD,[3] and Paul A. Meyers, MD[2]

12g/m2 en 4 h

TABLE I. The Memorial Sloan Kettering Leucovorin Rescue Algorithm

Time post-MTX administration	MTX level (μmol/L)	Leucovorin dose	Additional therapeutic modification
24 hrs.	≤10	10 mg po q6h	
	10–20	20 mg po q6h	
	20–30	30 mg po q6h	IV hydration may be increased
	30–50	50 mg po q6h	IV hydration may be increased
	≥50	1 g iv over 24 hrs.	Mandatory admission to hospital; hydration increased; frequent blood work and monitoring
48 hrs.	≤1	Continue previous 24-hrs. dosing	
	1 or greater	Consider dose escalation	
72 hrs.	≤0.1	Discontinue leucovorin	
	0.1 or greater	Continue previous 48 hrs. dosing	Reassess MTX level in 24 hrs. Discontinue leucovorin when MTX level is ≤0.1 μmol/L

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Prevention and Management of High Dose Methotrexate Toxicity

Yasar Albushra Abdul Rahiem Ahmed[1]* and Yasir Hasan[2]

Hammor and Hasan, J Cancer Sci Ther 2013, 5.3

AUTHOR/ YEAR	MTX DOSE	MTX INFUSION DURATION	LEUCOVORIN RESCUE DOSE	START OF LEUCOVORIN[A]
ALL				
Takeuchi 2002 [6]	100 mg/m² bolus, then 500 mg/m² as a 4-hour infusion	4 hours	15 mg every 6 hours for 8 doses	28 hours
Linker 2002 [7]	220 mg/m² bolus, then 60 mg/m² per hr x 36 hours	36 hours	50 mg/m² IV every 6 hours for 3 doses, then orally until serum MTX < 0.05 µM	36 hours
Han 2001 [8] Hill 2004 [9]	8 g/m² (age ≤ 4) 6 g/m² (age > 4)	10% bolus, remainder over 23 hours	15 mg/m² every 3 hours, then every 6 hours when serum MTX < 2 x 10⁶ µM	36 hours
Pui 2004 [10]	2 g/m²	2 hours	10 mg/m² every 6 hours	44 hours
Asselin 2011 [3]	5 g/m² (0.5 g/m² bolus over 30 minutes, then 4.5 g/m²over 23.5 hours)	24 hours	75 mg/m² then 15 mg/m² every 6 hours until serum MTX ≤ 0.1 µM	36 hours
CNS Lymphoma				
Ferreri 2009 [4] Joerger 2010 [11]	3.5 g/m² (0.5 g/m² in 15 minutes, then 3 g/m² as a 3- hour infusion)	3 hours, 15 minutes	15 mg/m² every 6 hours for 12 cycles or until serum MTX levels are undetectable	24 hours
Osteosarcoma				
Souhami 1997 [12]	8 g/m² (≥ 12 years old) 12 g/m² (< 12 years old)	Not specified	12 mg/m² IV or 15 mg/m² orally every 6 hours for 10 doses	24 hours
Fuchs 1998 [13]	12 g/m² (maximum 20 g)	Not specified	15 mg/m² every 6 hours for 12 doses	Not specified
Bacci 2001 [14]	12 g/m² (escalate to 14 g/m² if 6-hr serum MTX < 1 µM)	6 hours	15 mg every 6 hours for 11 doses	24 hours
Goorin 2003 [15]	12 g/m²	4 hours	15 mg every 6 hours for 10 doses	24 hours
Ferrari 2005 [16]	12 g/m²	4 hours	8 mg/m² every 6 hours for 11 doses	24 hours
Holmboe 2012 [17]	Mean dose, 12 g/m² (range, 8-16 g/m²)	4 hours	Standard dosing until serum MTX ≤ 0.2 µM	24 hours

*After start of MTX

ALL = acute lymphoblastic leukemia; CNS = central nervous system; HDMTX = high-dose methotrexate; IV = intravenous; MTX = methotrexate

Table 1: Sample HDMTX Protocols in Pediatric and Adult Cancers.

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