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Networking: *Controversias entorno a la intoxicación por metotrexato: Uso de la glucarpidasa*

Monitorización farmacocinética del metotrexato

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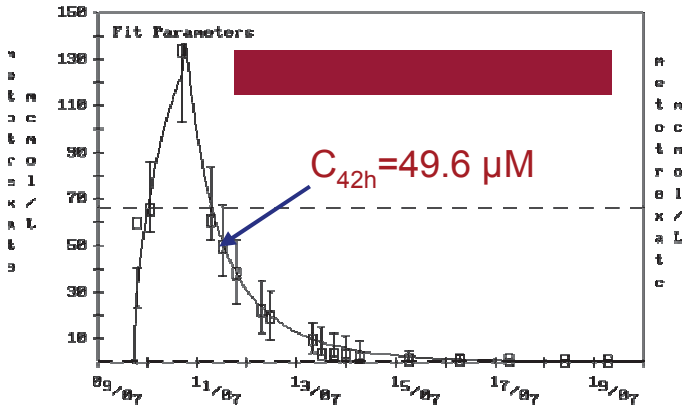
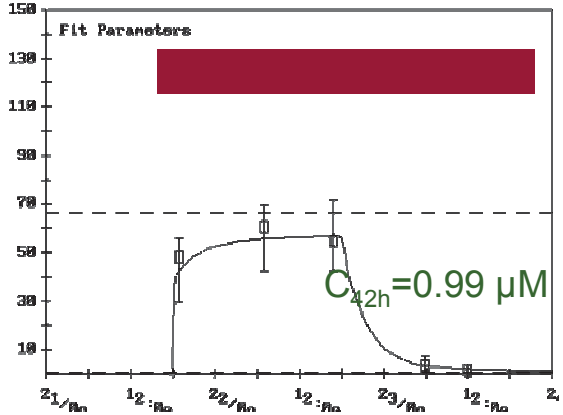
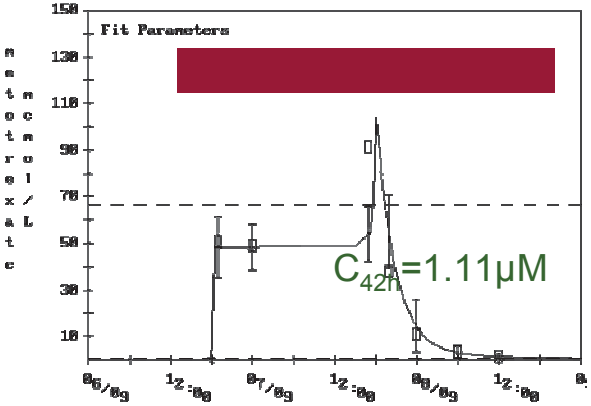
2 de octubre 2014

Caso clínico 1 - seguimiento

Dosis de MTX:				
Dosis (g/m^2)		3	3	3
Dosis (mg)		3500	3500	3600
[MTX] µM:				
24 h	<150	133.8	54.55	91.06
36 h	<3	60.12	3.10	3.36
42 h	<1	**49.46**	0.99	1.11
48 h	≤ 0.4	37.87		
61 h	<0.2	21.88	0.29	0.16
Horas hasta [MTX]<0.2 µM		**227**	84	60
Creatinina sérica (mg/dl)				
Basal		0.3	0.4	0.5
Valor máximo		3.8	0.7	0.63







Carboxypeptidasa ($CPDG_2$) ¿Cuándo?

Table 1: Threshold plasma MTX concentrations for Voraxaze administration

MTX Dose:	1 g/m^2	2 g/m^2	5 g/m^2	4 g/m^2	8 g/m^2	12 g/m^2
Infusion duration:		> 24 hours			> 4 hours	
Hours following start of MTX infusion	Threshold plasma MTX concentration (µmol/L)[a]					
12 hours	≥ 50	≥ 100	≥ 250	≥ 160	≥ 310	≥ 470
24 hours	≥ 50	≥ 100	≥ 250	≥ 25	≥ 50	≥ 75
36 hours	≥ 7.5	≥ 15	≥ 35	≥ 5	≥ 10	≥ 16
42 hours	≥ 3	≥ 6	≥ 16	≥ 3	≥ 6	≥ 9
48 hours	≥ 1.5	≥ 3	≥ 7.5	≥ 2	≥ 4	≥ 6
≥ 60 hours	≥ 1	≥ 1	≥ 2.5	≥1	≥ 2	≥ 3

Values have been … than 12 hours, val… … ed values below 1 µmol/L repla… …ictions for the end of infusion. …ater

Si C_{36h} > 50µM

Si C_{24h} > 50µM

[MTX sérica] ≥42h desde inicio infusión de MTX	[THF] deseada	Dosis de LV
20-50µM	200-500µM	500mg/m^2 IV/6h
10-20µM	100-200µM	200mg/m^2 IV/6h
5-10µM	50-100µM	100mg/m^2 IV/6h
1-5µM	5-10µM	30mg/m^2 IV o vo/6h
0.6-1µM	0.6-1µM	15mg/m^2 IV o vo/6h
0.1-0.5µM	0.1-0.5µM	15mg/m^2 vo/12h
0.05-0.1µM	0.05-0.1µM	5-10mg/m^2 vo/12h

…és de la … la

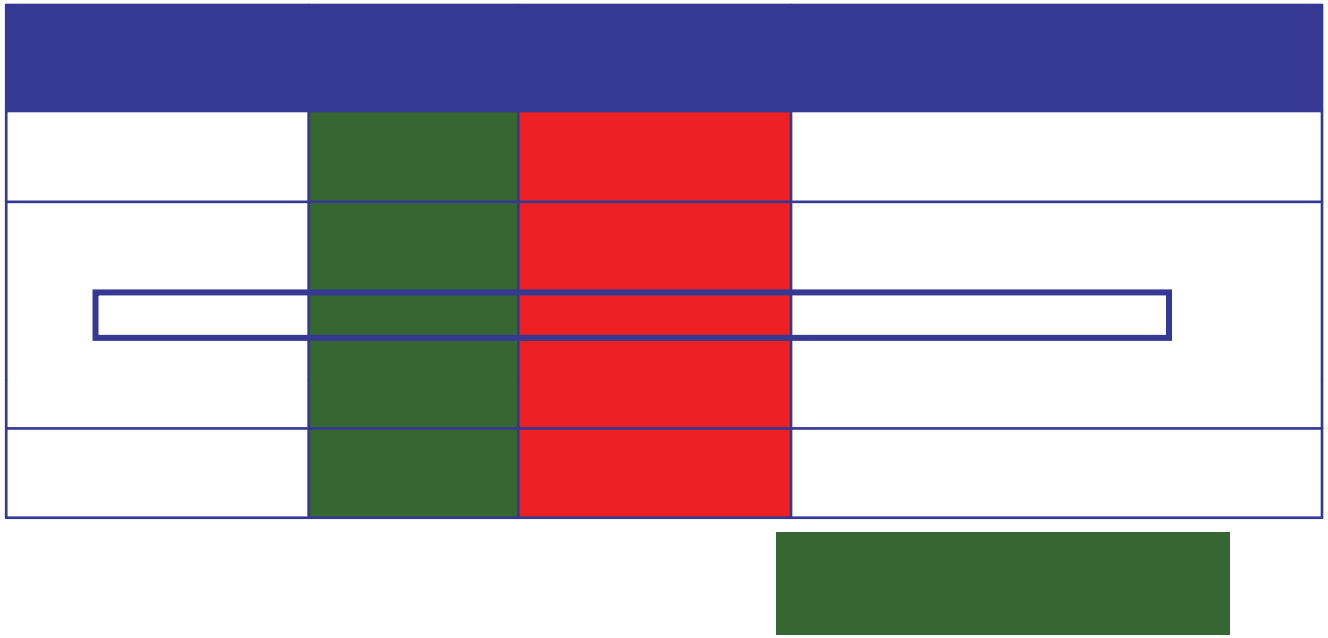
Evans WE, Shentag JJ, Jusko WJ. Applied pharmacokinetics. Principles of therapeutic Drug Monitoring. 3ª ed. Vancouver: Applied Therapeutic Inc. 1992.

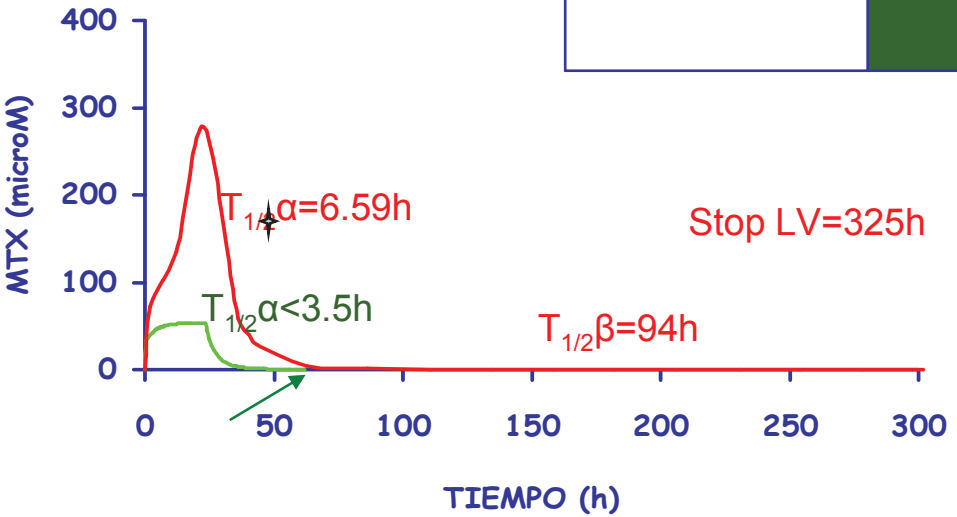
Caso clínico 2

Edad: 53 años varón
Diagnóstico: Linfoma del MALT

Si C_{36h}> 50µM

Protocolo: BONN: 5g/m² en 24h





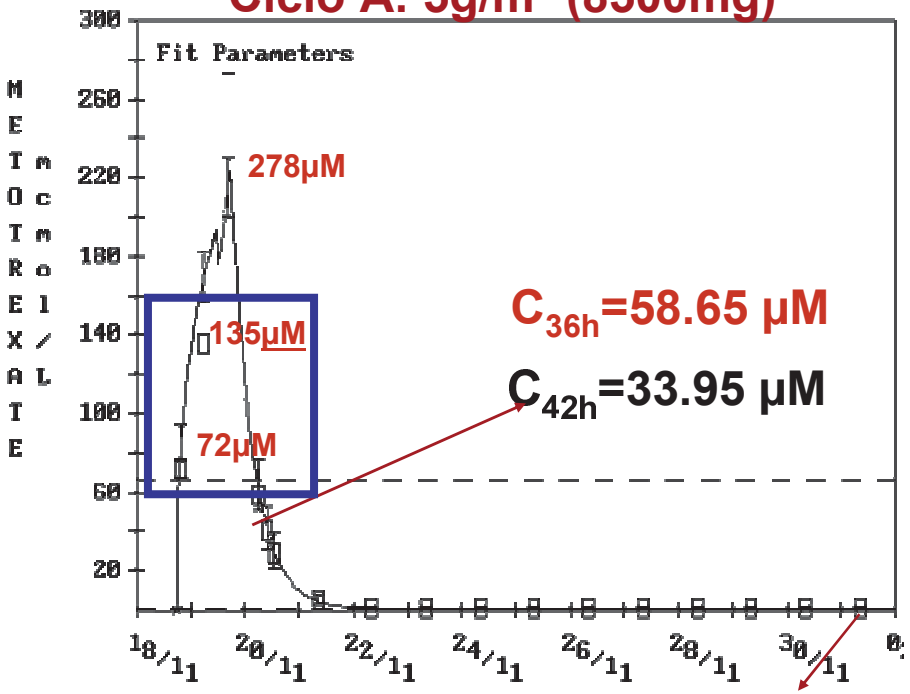
Stop LV=325h

Ac. Folínico:500mg/m²/3h a las 42h (2 dosis), luego c/6h, en pauta descendente según [MTX]
Hidratación: 3.5 L/m2
pH urinario: ≥ 7 en todo momento

Toxicidad
- Crs=2.67mg/dl (0.9mg/dl al alta)
- NO Mucositis
- AST/ALT=51/119 (gradol)

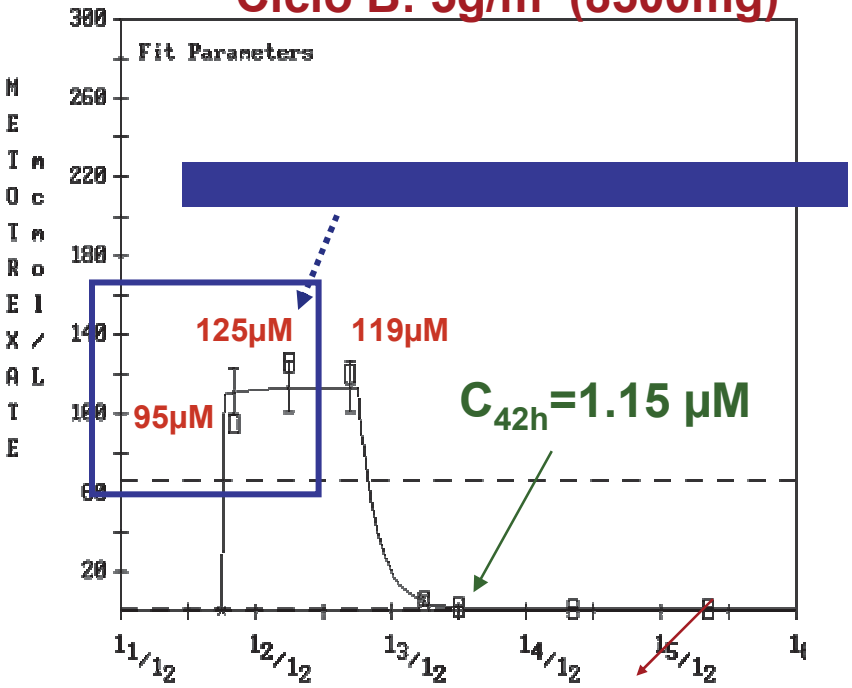
Caso clínico 2-seguimiento

Ciclo A: 5g/m² (8500mg)



Stop LV: 325 h
(13.5 días)

Ciclo B: 5g/m² (8500mg)



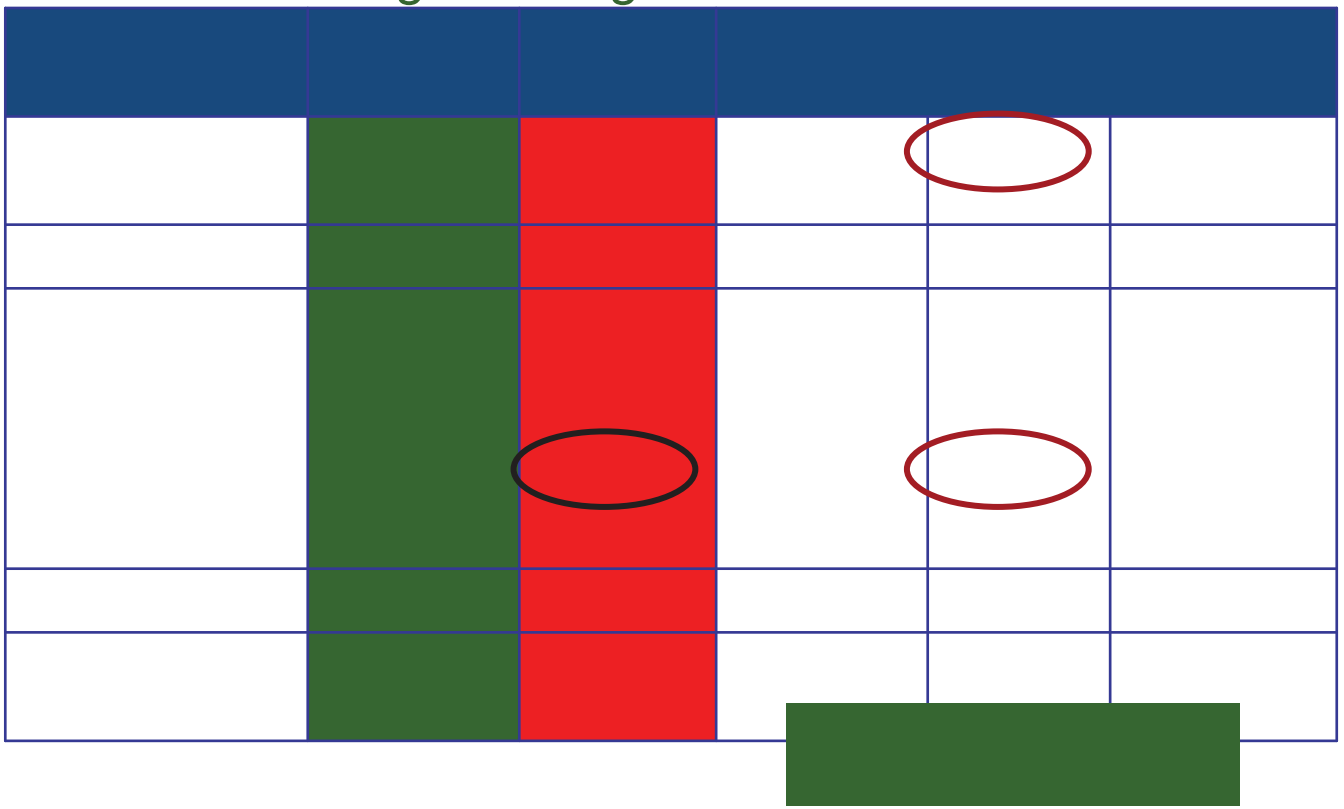
Stop LV: 84 h
(3.5 días)

Caso clínico 3

Edad: 44 años varon
Diagnóstico: Linfoma cerebral

Si C_{24h}> 50µM

Protocolo: D´Angelis: 2.5g/m^2 en 4 h



Toxicidad
- Crs=3.49mg/dl (1mg/dl al alta)
- Mucositis I
- Enzimas hepaticas normales

Ac. Folínico:500mg/m^2/6h a las 24h (4 dosis), luego en pauta descendente según [MTX]
Hidratación: 3 L/m2 (6000ml/día)
pH urinario: ≥ 7 en todo momento

Si C_{36h}> 50µM

Caso clínico 4

Edad: 22 años, varón
Diagnóstico: Linfoma células T/NK Tipo Nasal
Protocolo: SMILE

Dosis de MTX: 4000mg en 24h (2g/m²)
12:00h STOP --> recibió 3000mg en 18h

	Día 0 J. 29/08	Día 1 Vier 30/08	Día 2 Sáb 31/08	Día 3 Dom 01/09	Día 4 Lun 02/09	Día 5 Mar 03/09	Día 6 Mier 04/09	Día 7 Jue 05/09
Cp MTX (µM)	Inicio MTX 4000mg (18:00h)	C_{14h}=104.24 STOP 12:00h	C_{36h}= 51.32 C_{42h}= 44.21	C_{62h}=15.71	C_{86h}=4.15	C_{110h}=0.98	C_{134h}=0.32	C_{158h}=0.14
Hidratación	168 ml/h (4000ml)	84 ml/h (2000ml)	126 ml/h (3000ml)	126 ml/h (3000ml)	168 ml/h (4000ml)	168 ml/h (4000ml)	105 ml/h (2500ml)	84 ml/h (2000ml)
pH urinario (M,T,N)	6.5 / 6 / 7	6.5 / 6.5 / -	7.5 / 7.5 / 7	7 / 7 / 7	6 / 7 / 7	7 / 7 / 6	7 / 7 / 7	8 /
Lederfolin IV		15mg/m²/6h 18:00h 24:00	15mg/m²6:00h 75mg/m² 12:00h 500mg/m² 15:00h 18:00h y 24:00h	500mg/m²/6h	500mg/m²/6h	250mg/ m²/6h	30mg/ m²/6h	15mg/ m²/6h
Flilicol			3g/6h Inicio 18h	3g/6h	3g/6h	3g/6h Fin 12h		
Crs (mg/dl)	0.74	1.71 / 2.5	3.2	3.4	3.24	2.61	2.45	2.22
Diuresis	1900ml	4000ml	7200ml	7600ml	8000ml	4700ml	5300ml	4000ml
AST/ALT	467 / 911	678 / 728 830 / 897	933 / 867 1517 / 1041	2829 / 1505	3819 / 1779	1933 / 1117	1094 / 747	864 / 606

Mucositis III-IV

Melenas L=30

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Glucarpidase, Leucovorin, and Thymidine for High-Dose Methotrexate-Induced Renal Dysfunction: Clinical and Pharmacologic Factors Affecting Outcome

Brigitte C. Widemann, Frank M. Balis, AeRang Kim, Matthew Boron, Nalini Jayaprakash, Aiman Shalabi, Michelle O'Brien, Michelle Eby, Diane E. Cole, Robert F. Murphy, Elizabeth Fox, Percy Ivy, and Peter C. Adamson

J Clin Oncol 28:3979-3986. © 2010

Factores de riesgo de toxicidad:

- **Glucarpidasa>96 h**
- **Rescate inapropiado**
- **Toxidad grado IV previa**

Fallecen 12 pacientes:

- **6 por toxicidad por MTX**
- **6 por progresion de la enfermedad**

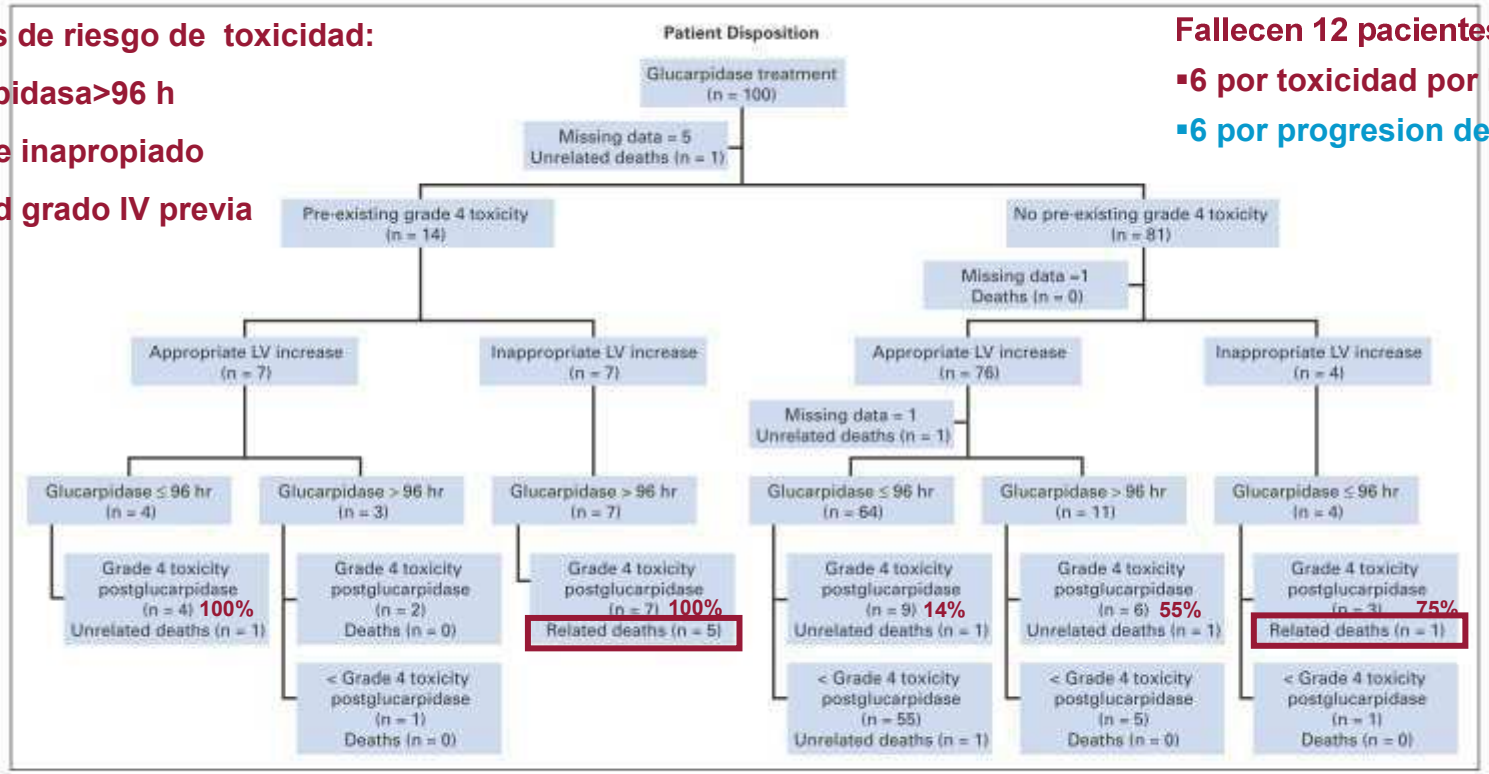


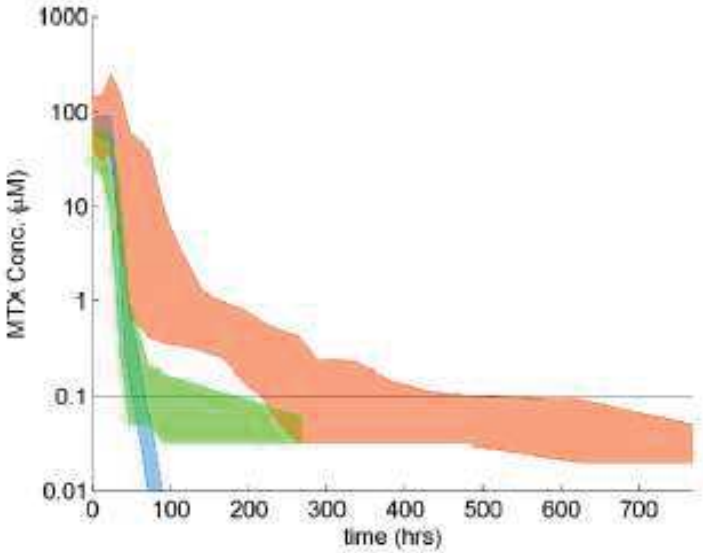
Fig 1. Disposition of 100 patients who received glucarpidase, indicating pre-existence or absence of grade 4 toxicity before administration of glucarpidase; appropriate or inappropriate increase in leucovorin (LV) rescue within 3 days after the start of high-dose methotrexate (HDMTX); timing of administration of glucarpidase at ≤ 96 hours or more than 96 hours after starting HDMTX; presence of grade 4 toxicity after the administration of glucarpidase; and death directly attributed or not directly attributed to MTX toxicity.

Networking: *Controversias entorno a la intoxicación por metotrexato: Uso de la glucarpidasa*

Resumption of High-dose Methotrexate after Acute Kidney Injury and Glucarpidase Use in Pediatric Oncology Patients

Anthony M. Christensen, Pharm.D.[1], Jennifer L. Pauley, Pharm.D.[1,2], Alejandro R. Molinelli, Ph.D.[3], John C. Panetta, Ph.D.[2,3], Deborah A. Ward, Pharm.D.[1,2], Clinton F. Stewart, Pharm.D.[2,3], James M. Hoffman, Pharm.D., M.S.[2,3], Scott C. Howard, M.D., M.S.[4,5], Ching-Hon Pui, M.D.[4,5], Alberto S. Pappo, M.D.[4,5], Mary V. Relling, Pharm.D.[2,3,4], and Kristine R. Crews, Pharm.D.[2,3,*]

Cancer. 2012 September 1; 118(17): 4321–4330. doi:10.1002/cncr.27378.



Characteristics of 20 patients at the time they received glucarpidase for delayed me 1,141 patients who received HDMTX.

	All Patients	Osteosarcoma	ALL	Other
Percent (No.) of patients who received glucarpidase	1.8% (20 of 1,141)	8% (6 of 75)	1.3% (10 of 741)	1.2% (4 of 325)
Plasma MTX concentrations by TDx				
20 – 24 hrs post-MTX (M)				
Median	138.0	353.1	114.42	99.2
Range	29.2 – 462.9	158.8 – 462.9	65.7 – 222.1	29.2 – 258
Time to 1st glucarpidase dose (hrs)		24-28h	44-48h	
Median	45.9	30	47.8	45.9
Range	26.3 – 95	28 – 46.5	26.3 – 95	28.8 – 48
Prior to glucarpidase (M)				
Median	29.1	267.3	18.1	54.6
Range	1.3 – 590.6	32.2 – 590.6	1.3 – 222.1	16.5 – 239.8
Time to complete MTX excretion (hrs)				
Median	355	407	344	415
Range	244 – 763	295 – 763.2	245 – 497	259.2 – 540

Si T_{inf}=4h ⟶ C_{20h}>200 μM

Si T_{inf}=24h ⟶ C_{36h}>100 μM

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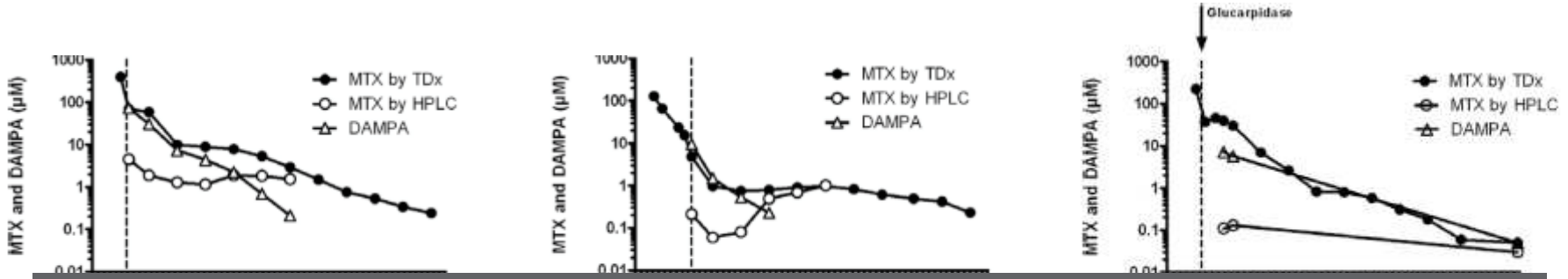
Cancer. 2012 September 1; 118(17): 4321–4330. doi:10.1002/cncr.27378.

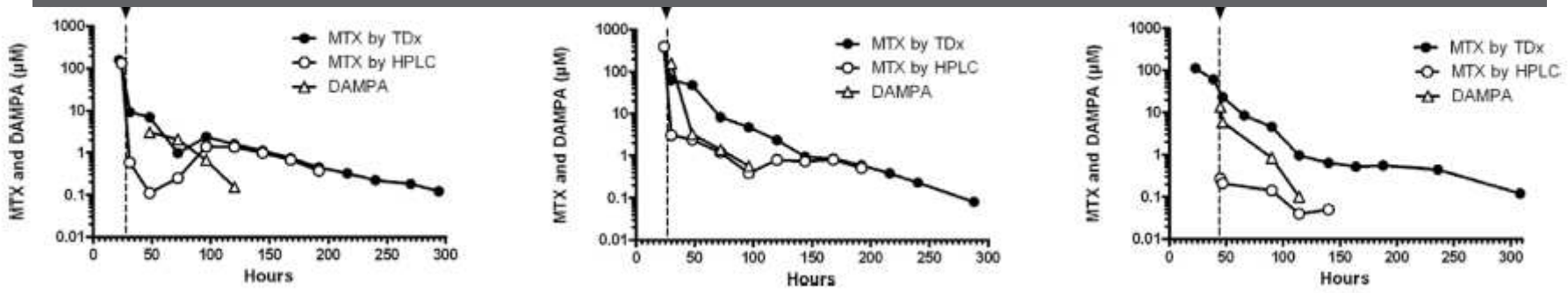
$CPDG_2$ y DAMPA muestran reactividad cruzada con el MTX determinado por inmunoensayos como el FPIA

DAMPA : $T_{1/2}$=9-12h —26%→ **[DAMPA] <1µM a los 4 días**

$CPDG_2$: $T_{1/2}$=9 h —59%→ **[$CPDG_2$] se elimina en 8 horas**



However, in the absence of an HPLC assay, commercial methods can be used to guide the duration of leucovorin rescue because DAMPA metabolite levels become insignificant as the plasma methotrexate concentration approaches 0.1 µM



Efficacy of Glucarpidase (Carboxypeptidase G2) in Patients with Acute Kidney Injury After High-Dose Methotrexate Therapy

Brigitte C. Widemann,[1] Stefan Schwartz,[2] Nalini Jayaprakash,[1] Robbin Christensen,[3] Ching-Hon Pui,[3] Nikhil Chauhan,[4] Claire Daugherty,[4] Thomas R. King,[4*] Janet E. Rush,[4] and Scott C. Howard[3]
[1]National Cancer Institute, Bethesda, Maryland; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]St. Jude Children's Research Hospital, Memphis, Tennessee; [4]BTG International Inc., West Conshohocken, Pennsylvania

(Pharmacotherapy 2014;34(5):427–439) doi: 10.1002/phar.1360

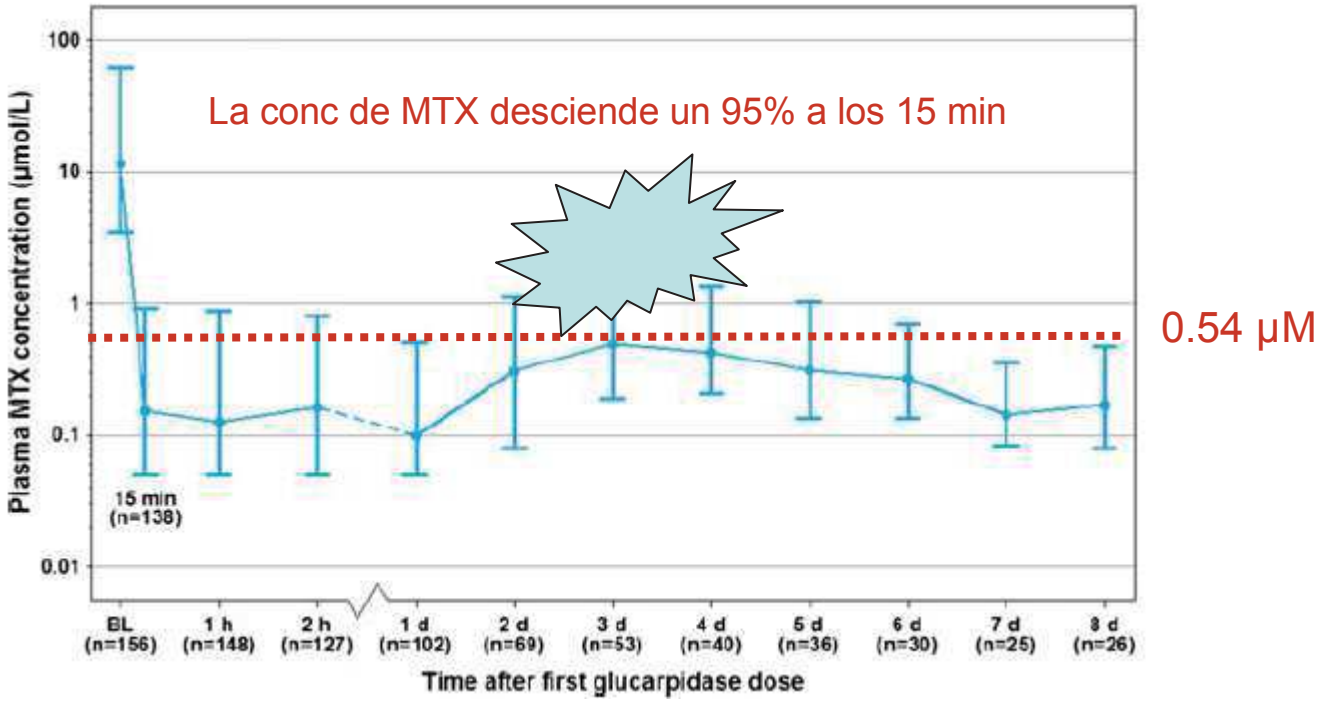


Figure 1. Methotrexate (MTX) concentrations (median [25th and 75th percentiles]) after treatment with glucarpidase in 156 of 169 efficacy-evaluable patients who had preglucarpidase (baseline [BL]) and postglucarpidase MTX measurements by high-performance liquid chromatography.

Consideraciones finales

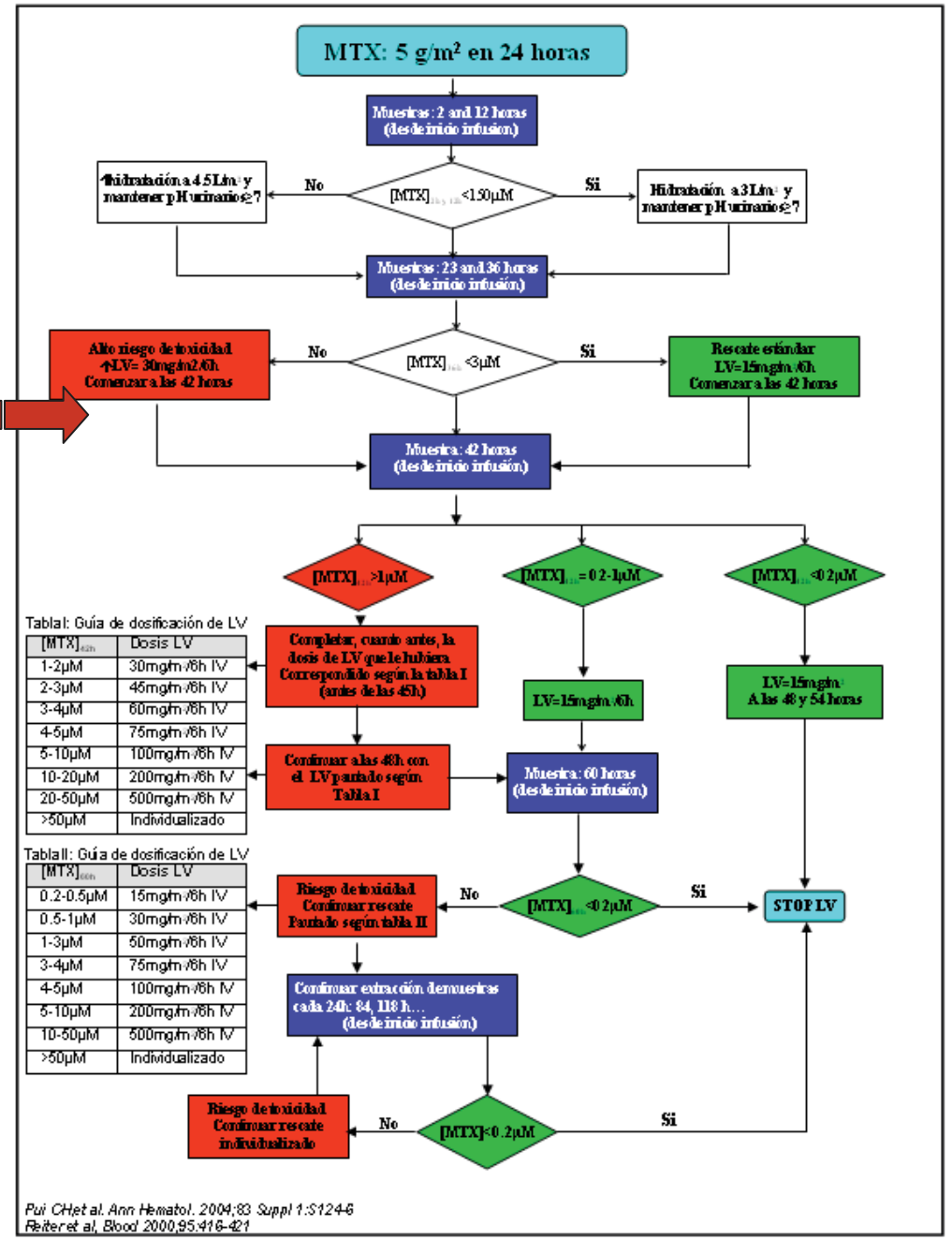
Para evitar la toxicidad severa por MTX

✓Identificar los pacientes de alto riesgo de intoxicación mediante estrategias de monitorización PK adecuadas, para corregir el rescate con LV a tiempo (antes de las 42 horas).

✓Si conc de MTX es excesivamente alta??? administrar glucarpidasa entre las 42-48h

Si T_{inf}=24h ⟶ C_{36h}>100µM

Si T_{inf}=4h ⟶ C_{20h}>200 µM



"Lo cierto siempre es penúltimo", porque lo último nunca lo sabremos, y siempre será una opción personal, con riesgo de estar equivocada

José Aumente, 1991

¡ Muchas gracias!