MANAGEMENT OF PRIMARY CNS LYMPHOMA

Shawn Kothari MD

July 21, 2023

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

AGENDA

1. Treatment Paradigm for Newly Diagnosed PCNSL
2. Methotrexate PK/PD

PRIMARY CNS LYMPHOMA – TREATMENT PARADIGM

INDUCTION

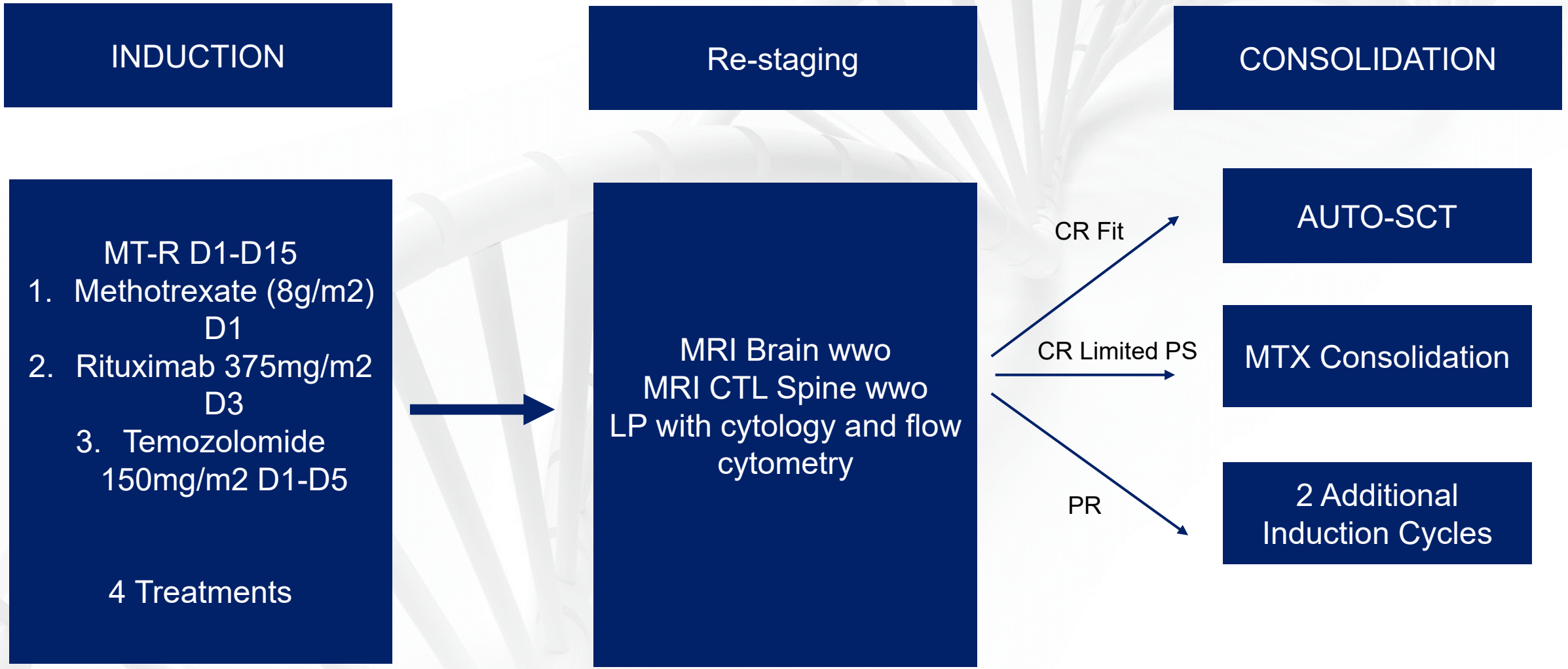
Polychemotherapy with CNS Penetrant Agents

Methotrexate
Alkylating Agents (Temzolomide, Procarbazine)
HD-AraC

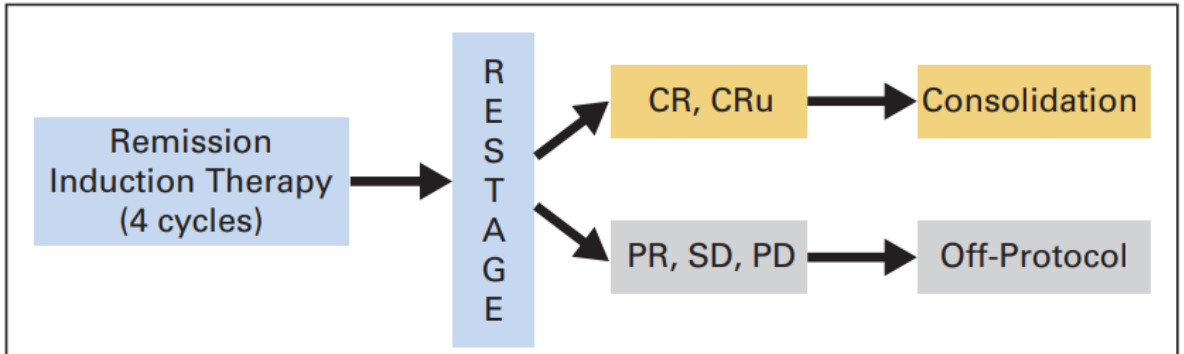
CONSOLIDATION

1. WBRT
2. Auto-SCT
3. Non-myeloablative Chemotherapy

PRIMARY CNS LYMPHOMA TREATMENT PARADIGM AT EMORY



MTR AS AN INDUCTION REGIMENT IN PRIMARY CNS LYMPHOMA – CALGB 50202



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m² IV over 4 hrs
Day 2	Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m² IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m² PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs × 8 doses

CR = 66%

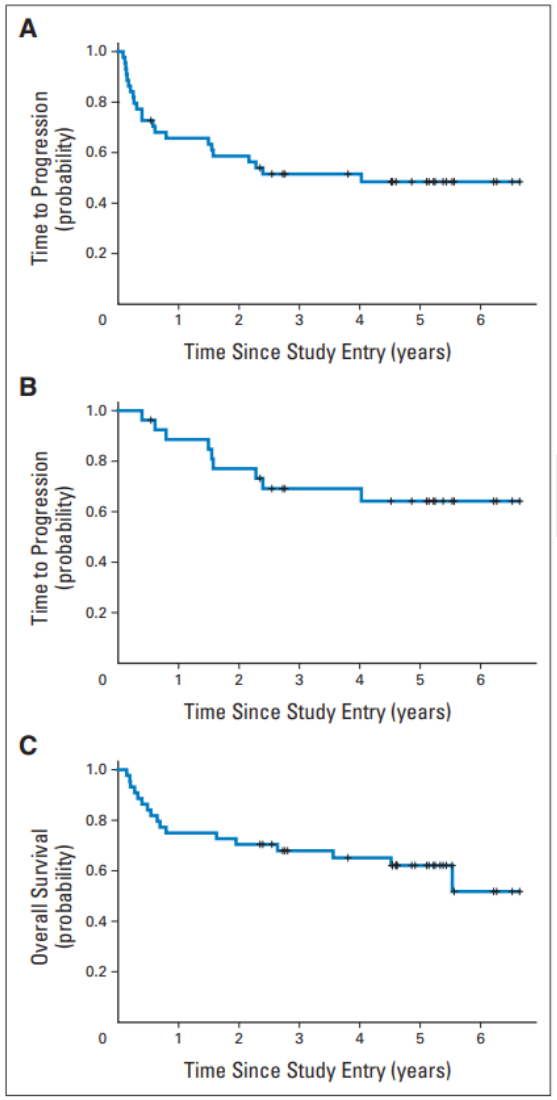


Table 2. Common Toxicities by Grade Occurring in Each Arm*

	Grade 3		Grade 4		Grade 5	
AE	No.	%	No.	%	No.	%
Maximum overall AE						
MT-R	24	55	12	27	0	0
EA	1	4	21	81	1	4

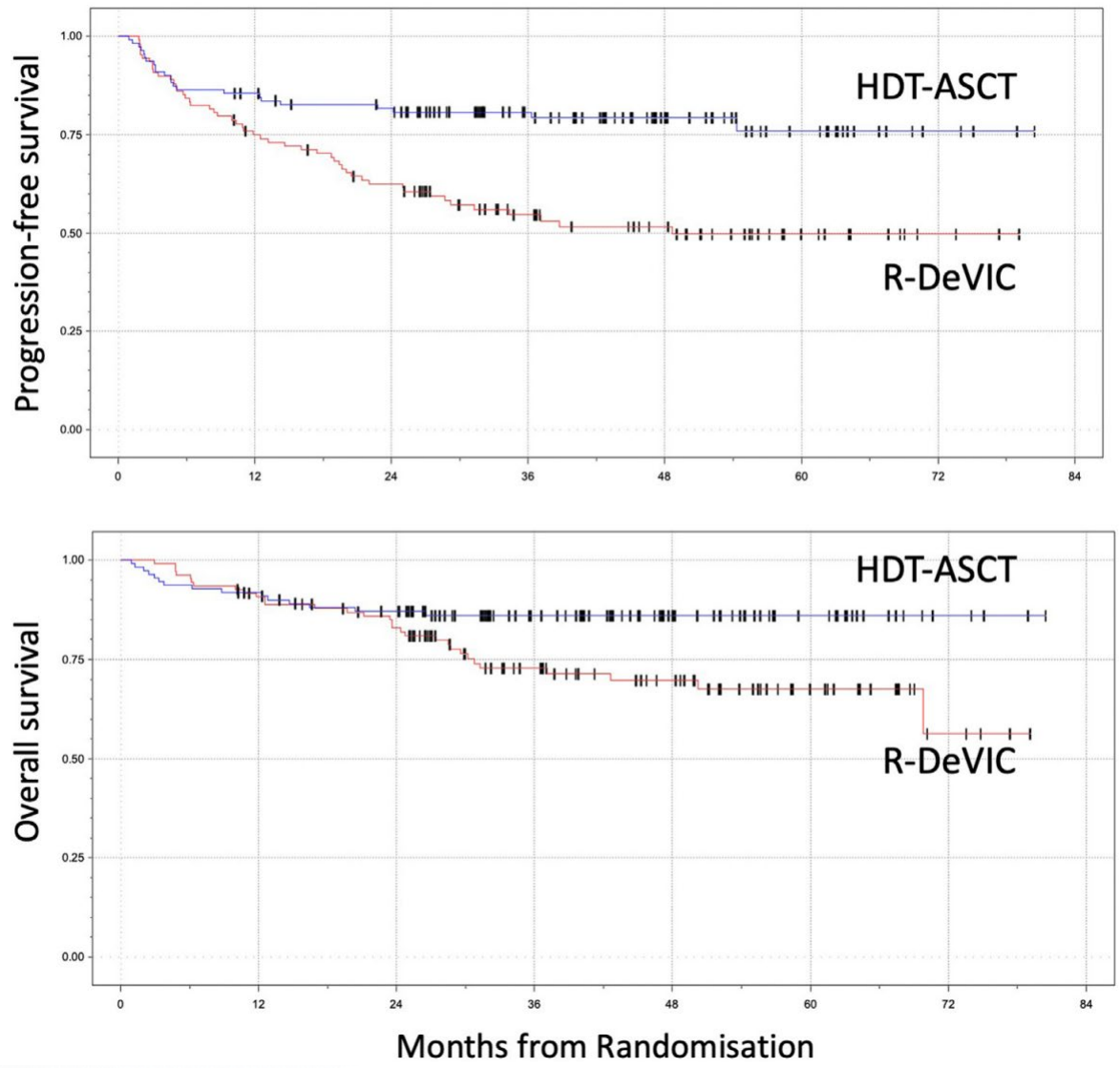
Rubinstein et al. JCO 2013

GROWING DATA FOR AUTO-SCT AS A CONSOLIDATION STRATEGY IN PCNSL

Late Breaking Abstract – ASH 2022

Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation (HDC-ASCT) As Consolidation Therapy in Patients with Primary CNS Lymphoma
Illerhause et al.

CONCLUSION: This international randomized phase III trial demonstrates that **consolidation with HDC-ASCT results in significantly better outcome than non-myeloablative chemoimmunotherapy. This comes along without any measurable negative effect on neurocognitive functions and with an excellent risk-to-benefit ratio.** HDC-ASCT is the standard consolidation therapy for fit PCNSL patients



METHOTREXATE BASED CONSOLIDATION

INDUCTION

MT-R (2 cycles)

Methotrexate (8g/m2) D1 and D15

Rituximab 375mg/m2 D3 and D17

Temozolomide 150mg/m2 D1-D5

CONSOLIDATION

MT (10 cycles)

Methotrexate (8g/m2) D1

Temozolomide 150mg/m2 D1-D5

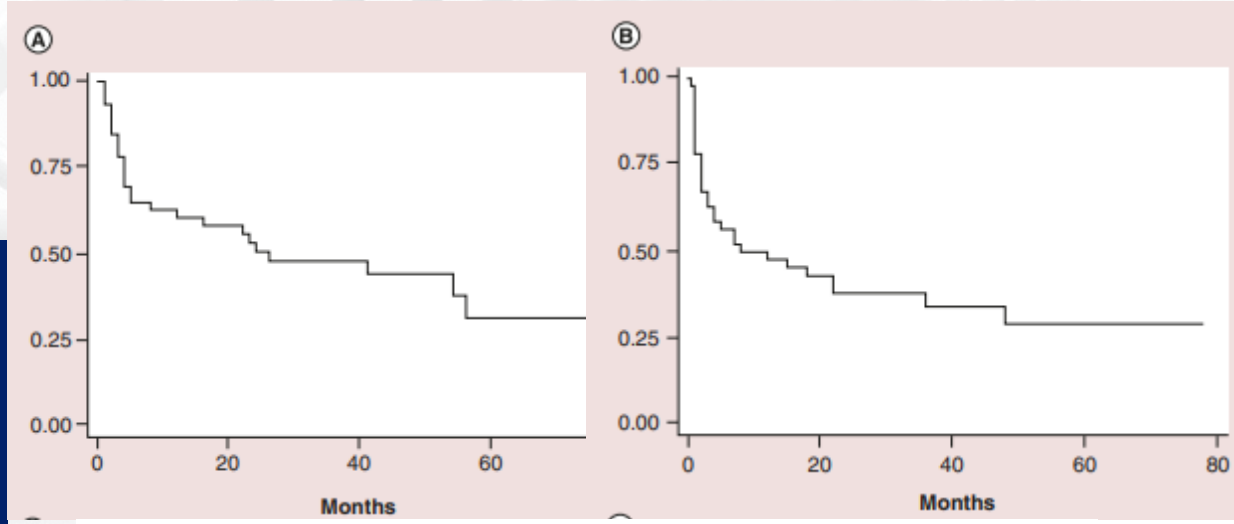


Table 3. Toxicities.

Toxicity	Number of patients	%
Acute kidney injury:		
– Grade 1	5	11
– Grade 2	12	26
– Grade 3	3	7
Transaminitis:		
– Grade 2	1	2
– Grade 3	6	13
Neutropenic sepsis:		
– Grade 4	4	9
Mucositis[†]	1	2
Pneumonitis[†]	1	2

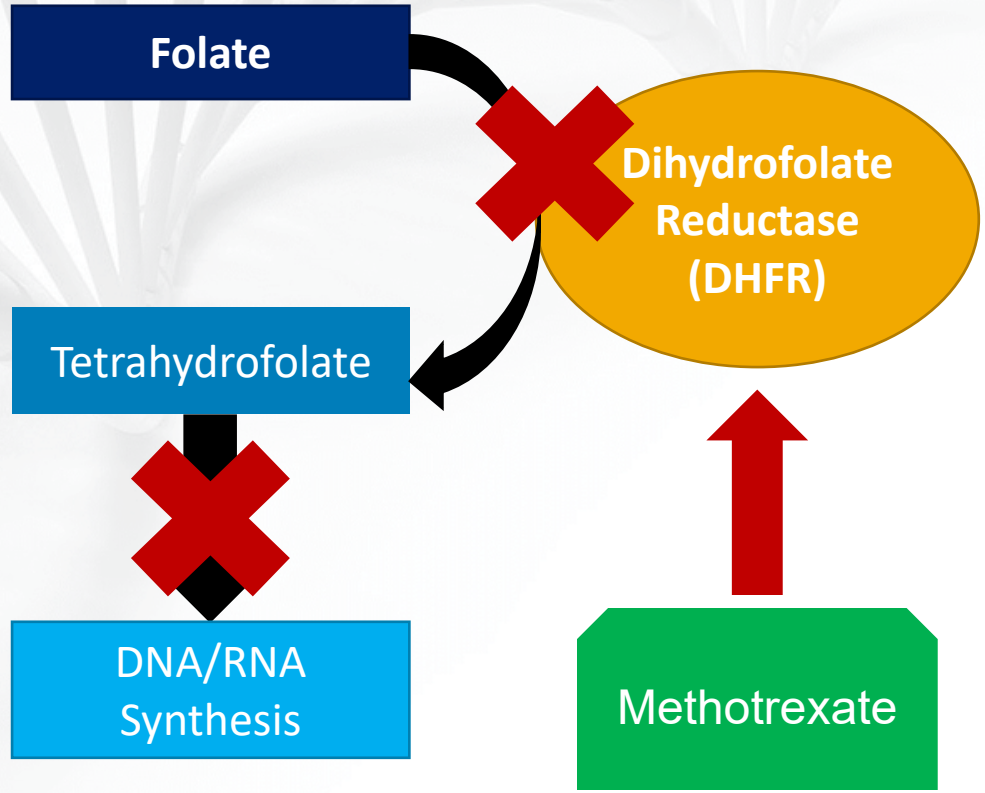
[†]Unable to be graded.

Nagle et al. *International Journal of Hematologic Oncology* 2017

METHOTREXATE (MTX)

- Folate antimetabolite
- Interferes with folic acid metabolism
- Leads to inhibition of tetrahydrofolate, which is necessary for DNA synthesis leading to cell death
- Pharmacokinetics:

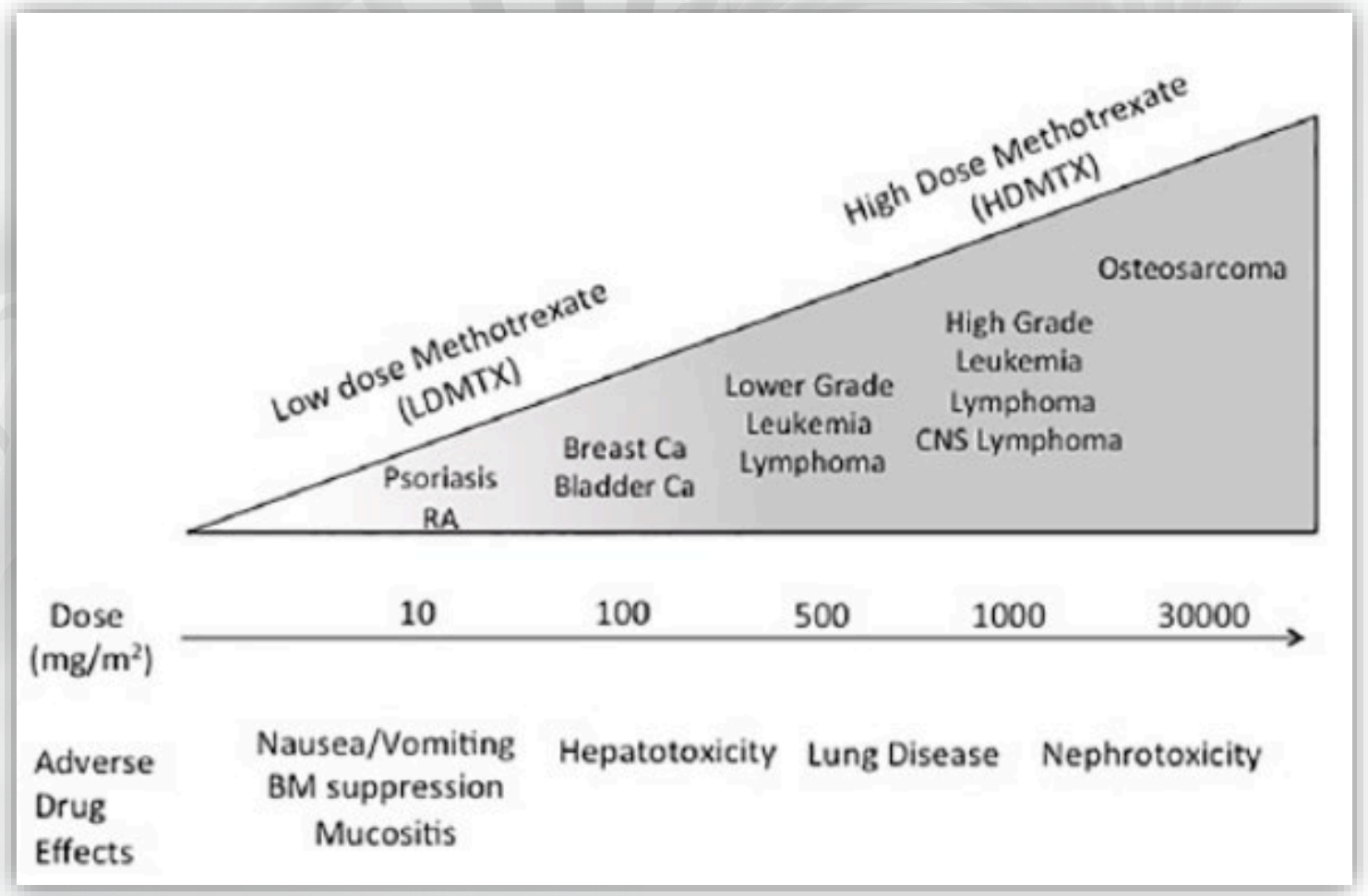
Absorption	IV/IM: 100% PO: variable/dose dependent (dec. at higher does)
Distribution	Penetrates slowly into third space fluids and exits slowly, sustained concentrations retained in kidney and liver, ~50% protein bound
Half Life	Low dose (PO): 3 to 10 hours High dose (IV): 8 to 15 hours
Metabolism	Intestinal flora (PO) and hepatic
Excretion	IV: Urine 80-90% as unchanged drug



Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

TOXICITIES ASSOCIATED WITH HDTMX

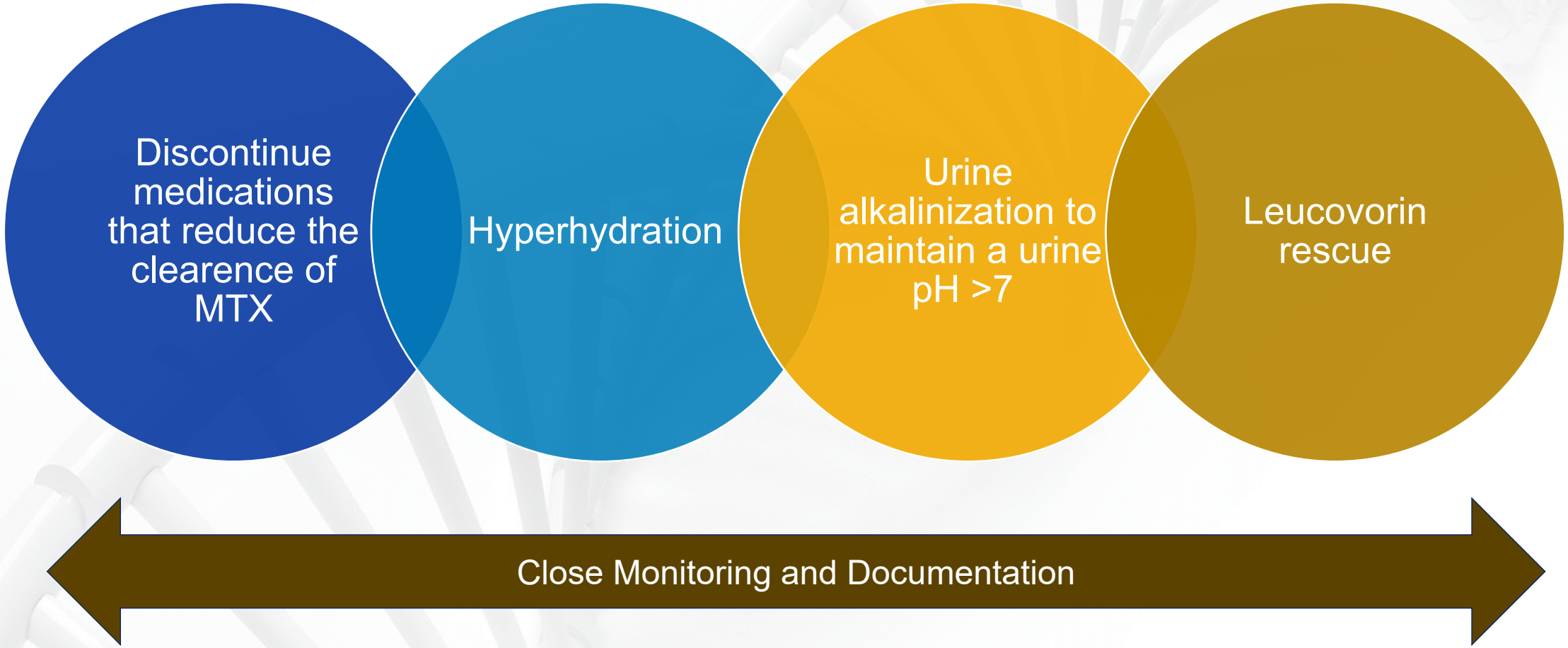
- GI Toxicity/Mucositis
- Myelosuppression
- Hepatotoxicity
- Acute Kidney Injury (AKI)
- CNS Disturbances
- Pulmonary Toxicity
- Multi-Organ Failure



Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Rubenstein, JK, et al. *Blood*. 2013 Oct 3; 122(14): 2318–2330.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

Ca: Cancer, RA: Rheumatoid arthritis

PREVENTION OF HDMTX TOXICITY

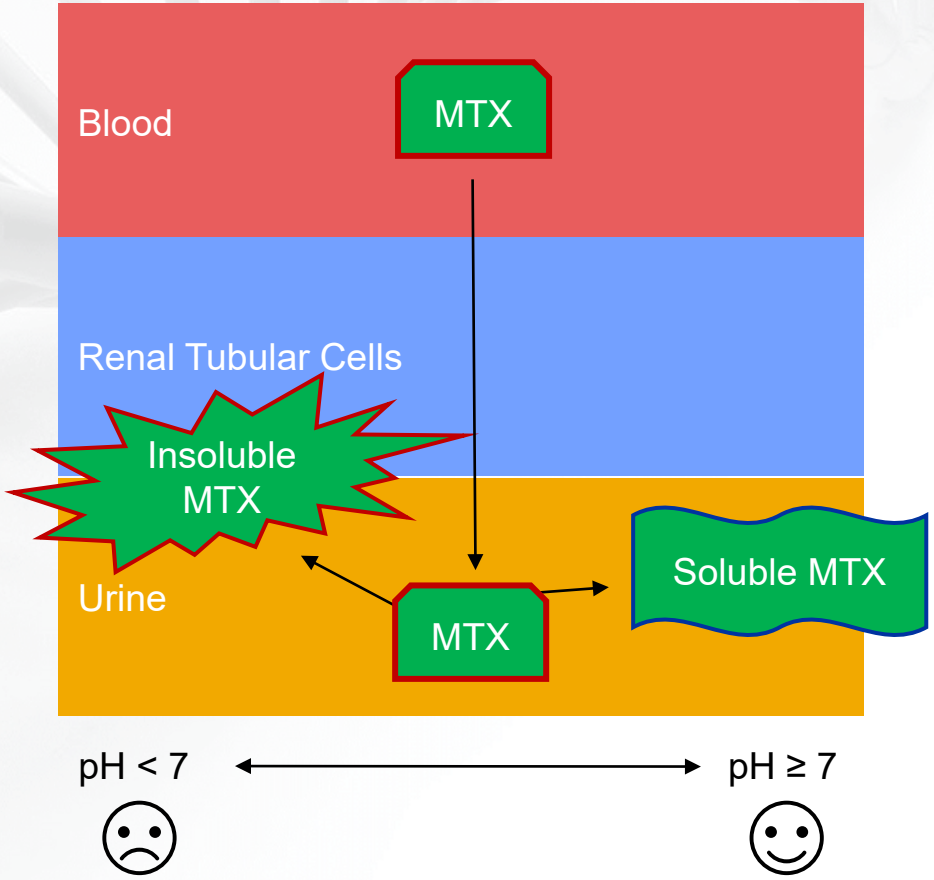


Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.

URINE ALKALINIZATION

Why?

- MTX is acidic and poorly soluble at a low/acidic pH
- Alkalization of the kidneys greatly increases MTX solubility and excretion
- Goal urine pH: 7-9



Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

URINE ALKALINIZATION

How?

- Counsel patient to avoid fruit juices and carbonated beverages
- Na bicarbonate tablets may be prescribed to start 48 hours prior to admission for HDMTX
- Na bicarbonate is added to IV fluids
- Na bicarbonate 1300mg tablets PO QID is started prior to MTX administration and continued until MTX lvl <0.1microM/L

Monitoring

- Urine pH after every void
- Do NOT start MTX until urine pH is ≥7 for at least two occasions at least 4 hours apart (and UOP ≥400 mL/4 hrs)

If urine pH <7 *after* starting MTX

- Administer Na bicarbonate 8.4% injection 50mEq IV push
- Administer acetazolamide 250mg PO BID
- Increase IV fluids to 200mL/hr
- Recheck urine pH after next void, if still pH <7, contact attending physician
- Investigate other sources (acidic beverages/DDI)

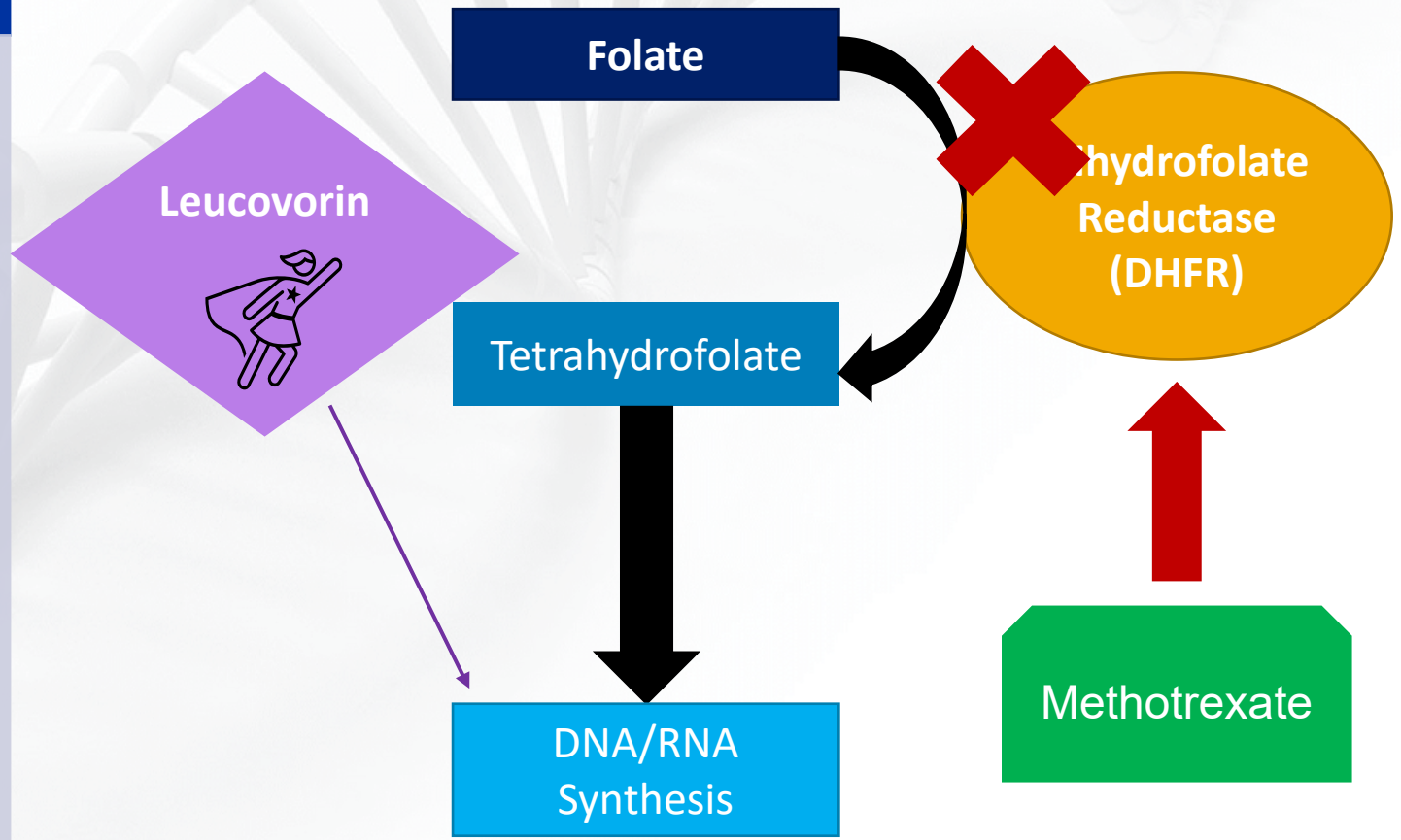
QID: Four times daily, BID: Twice daily

Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

LEUCOVORIN RESCUE

Why?

- Leucovorin is a folate metabolitee
- Effectively a bypass of Methotrexate, neutralizing the effects of MTX
- If started too early, it can reduce the anticancer efficacy of MTX
- LV is usually started 24 hours from the *start* of the MTX infusion
- It is important to monitor serum MTX levels per protocol because LV dosing is adjusted based on serum MTX levels

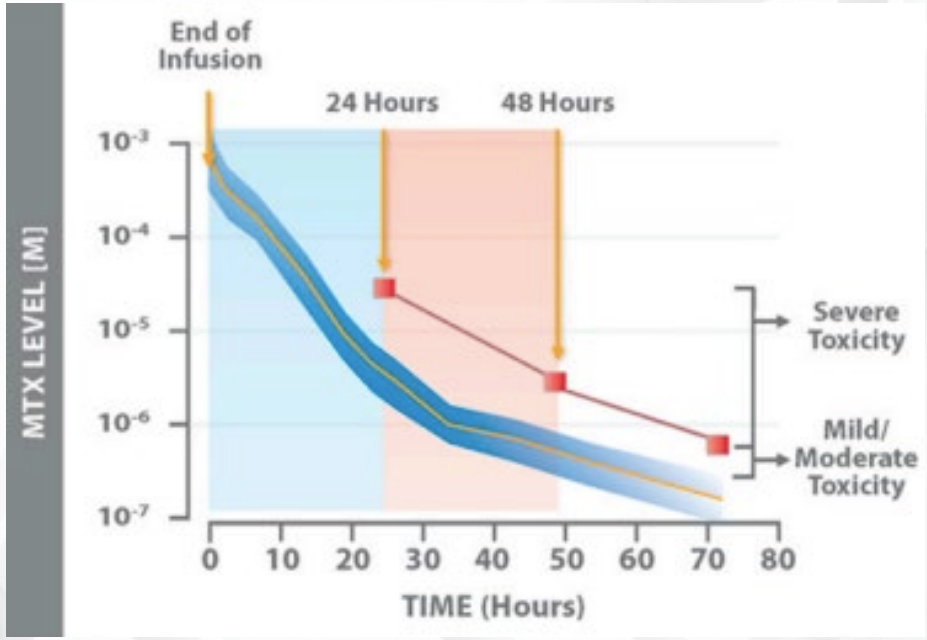


LV: Leucovorin; GI: Gastrointestinal

Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

MONITORING

- Draw MTX LVLs every 24 hours from the *start* of the MTX infusion until MTX LVL is ≤ 0.1 microM/L
- If MTX LVL ≤ 0.1 microM/L, discontinue all Na bicarbonate containing IV fluids/tablets, acetazolamide, and LV doses



0 hrs
Start of IV MTX infusion

24 hrs
Start LV 100mg IV q6hr
MTX LVL by peripheral blood draw*
- If >20, obtain stat redraw via peripheral blood draw
- If ≥10, change LV to 100 mg/m2 IV q6hr
- If <10, CCT

48 hrs
MTX LVL
- If ≥2, change LV to 200 mg/m2 IV q6hr
- If ≥1, change LV to 100 mg/m2 IV q6hr
- If <1, CCT

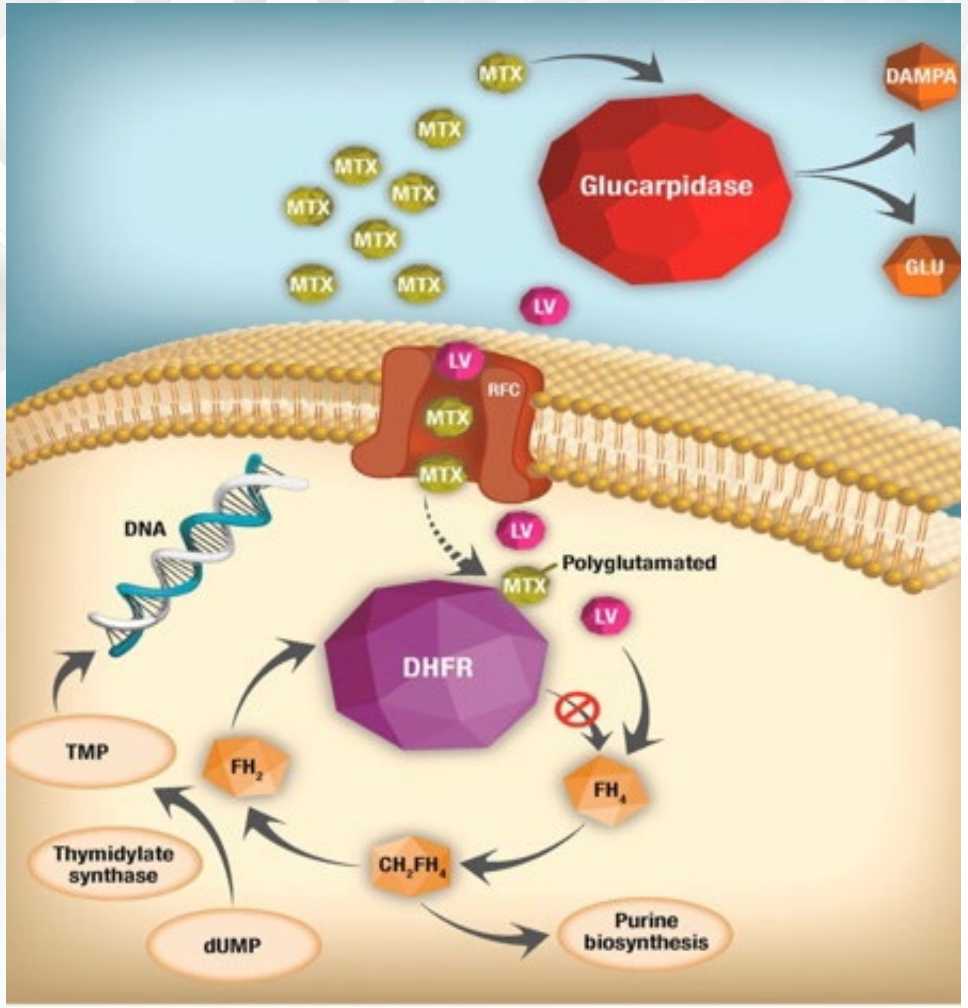
72 hrs
MTX LVL
- If >0.1, change LV to 100 mg/m2 IV q6hr

*Must draw first level by peripheral blood draw, may use iV cath for subsequent samples
MTX LVL: Methotrexate level, units: micromol/L; CCT: Continue current therapy; Na: Sodium

Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.

TREATMENT OF HDMTX TOXICITY

- **Glucarpidase:** metabolizes MTX to its inactive metabolites
- **Indication:** management of toxic plasma MTX concentrations (>1 microM/L) in adults and pediatrics with a delayed clearance* due to renal dysfunction
- **Caveats:**
  - Will not reverse toxicities present prior to administration
  - No effect on intracellular MTX concentration



*MTX plasma concentration >2 standard deviations of the mean MTX excretion curve specific for MTX dose administered

Howard SC, et al. *The Oncologist.* 2016 Dec;21(12):1471-1482.
Lexi-drugs online. Hudson (OH): Lexicomp, Inc.; 2016. Available from: http://online.lexi.com.