

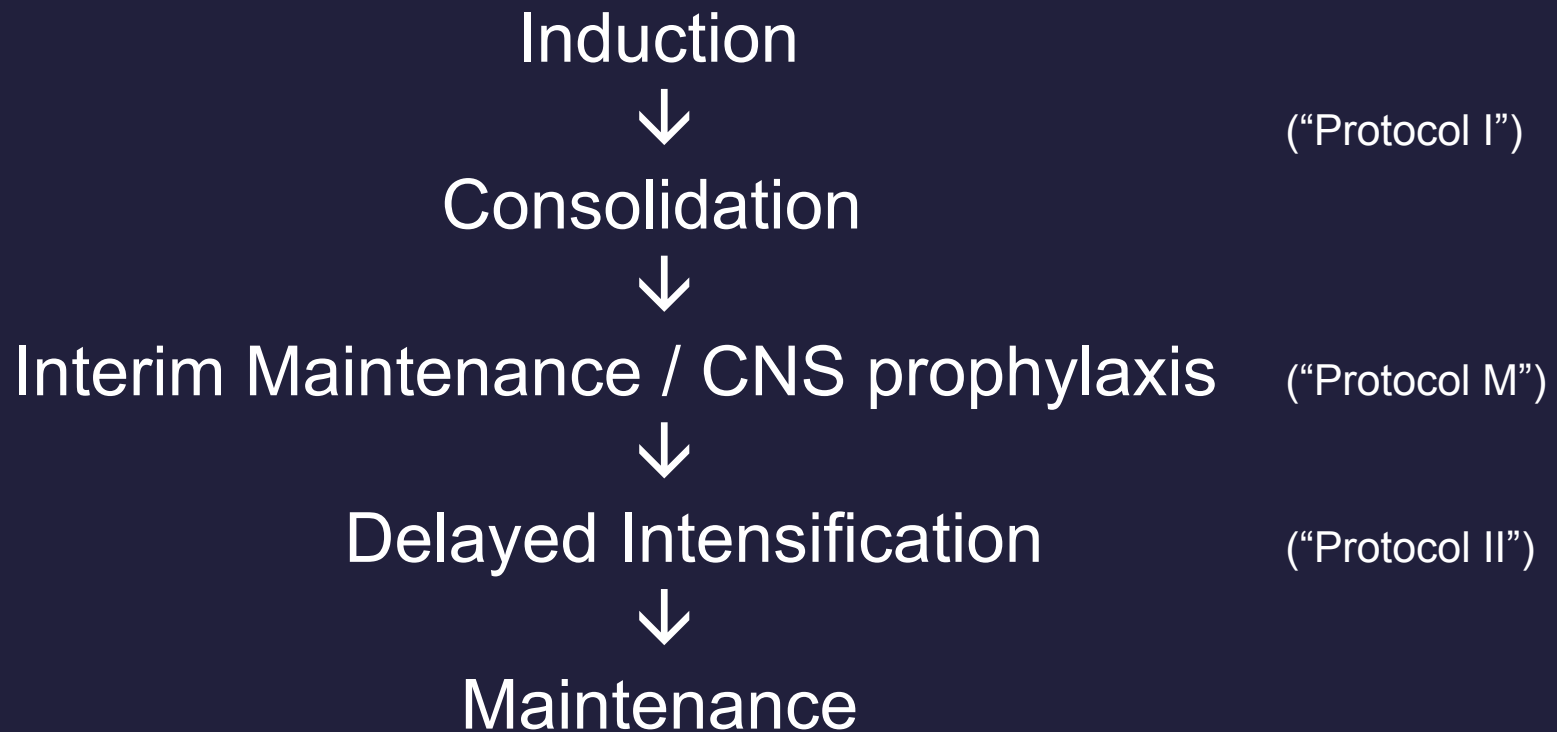
# Tolerance of anti-metabolite chemotherapy in childhood acute lymphoblastic leukaemia

Dr Andrew Moore

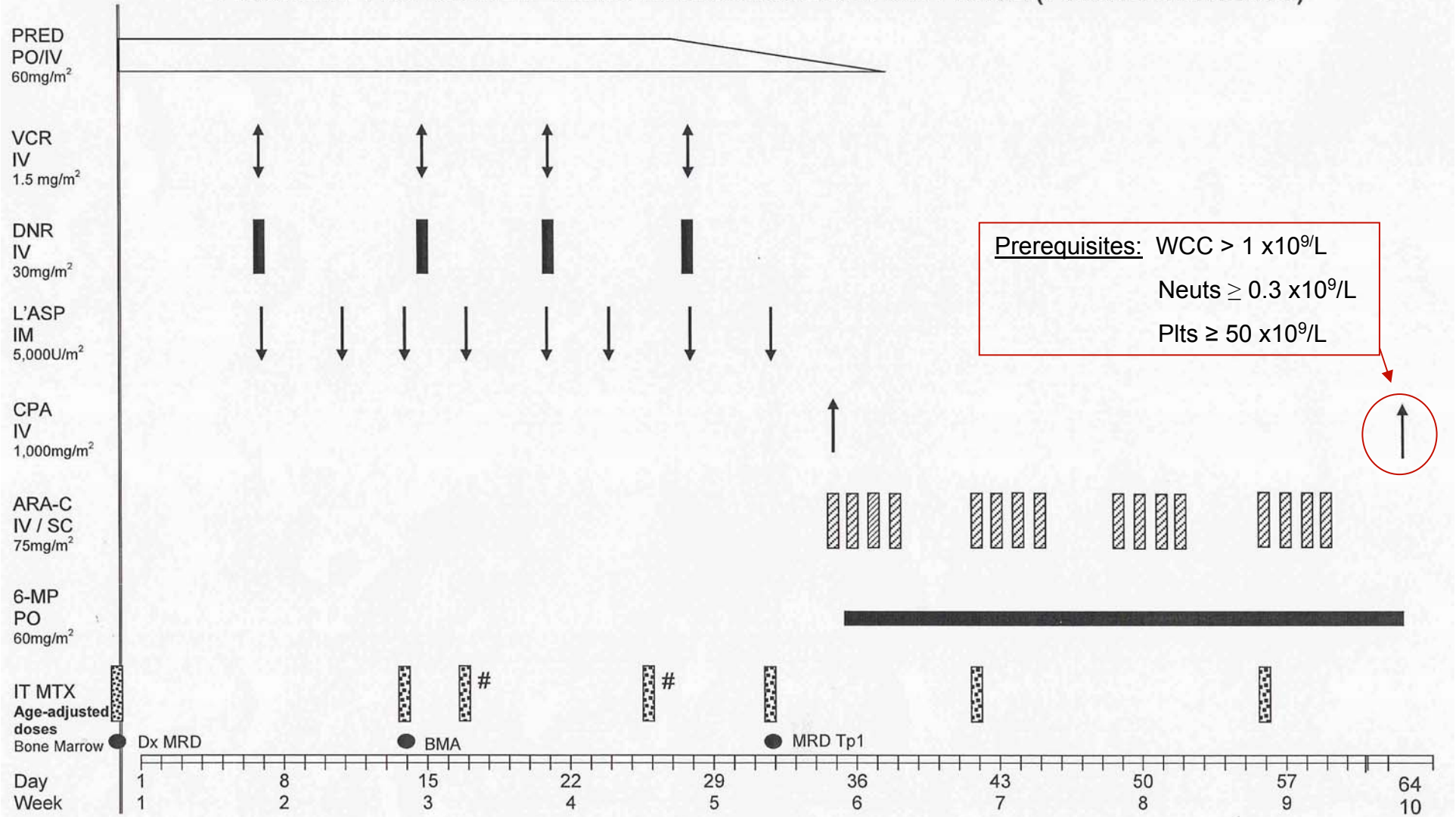
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# Background

- Treatment of childhood ALL involves multiple drugs used in varying combinations in different phases:



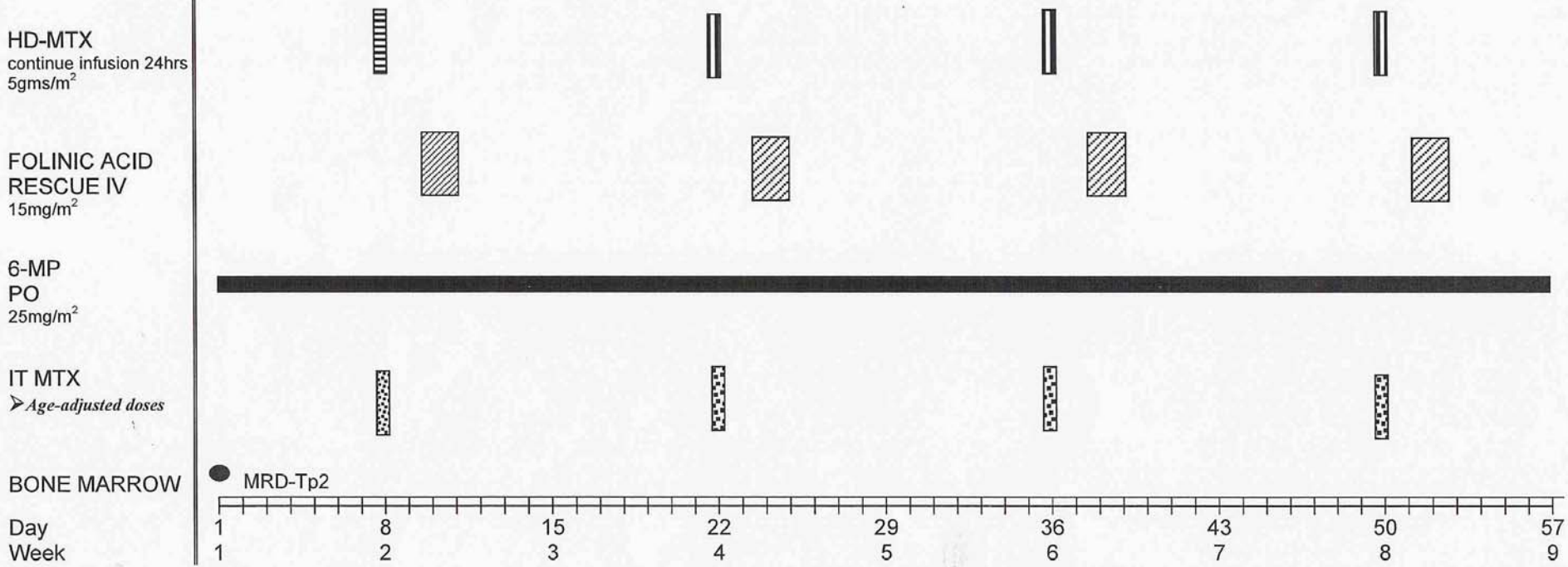
**FIGURE 4: PROTOCOL I: INDUCTION/CONSOLIDATION PHASE (FOR ALL PATIENTS)**



IT MTX Age-adjusted Doses: 1y:8mg / 2y:10mg / >=3y:12mg

# If CNS Disease at diagnosis (see protocol details)

**FIGURE 5: PROTOCOL M THERAPY FOR SR AND MR PATIENTS**



➤ Age-adjusted doses: 1y:8mg/ 2y:10mg/ >=3y:12mg

**FIGURE 6: PROTOCOL II THERAPY FOR ALL RISK GROUPS**

DEXA  
PO  
10mg/m<sup>2</sup>

VCR  
IV  
1.5 mg/m<sup>2</sup>

DOX  
IV 1hr  
30mg/m<sup>2</sup>

L'ASP  
IM  
10,000U/m<sup>2</sup>

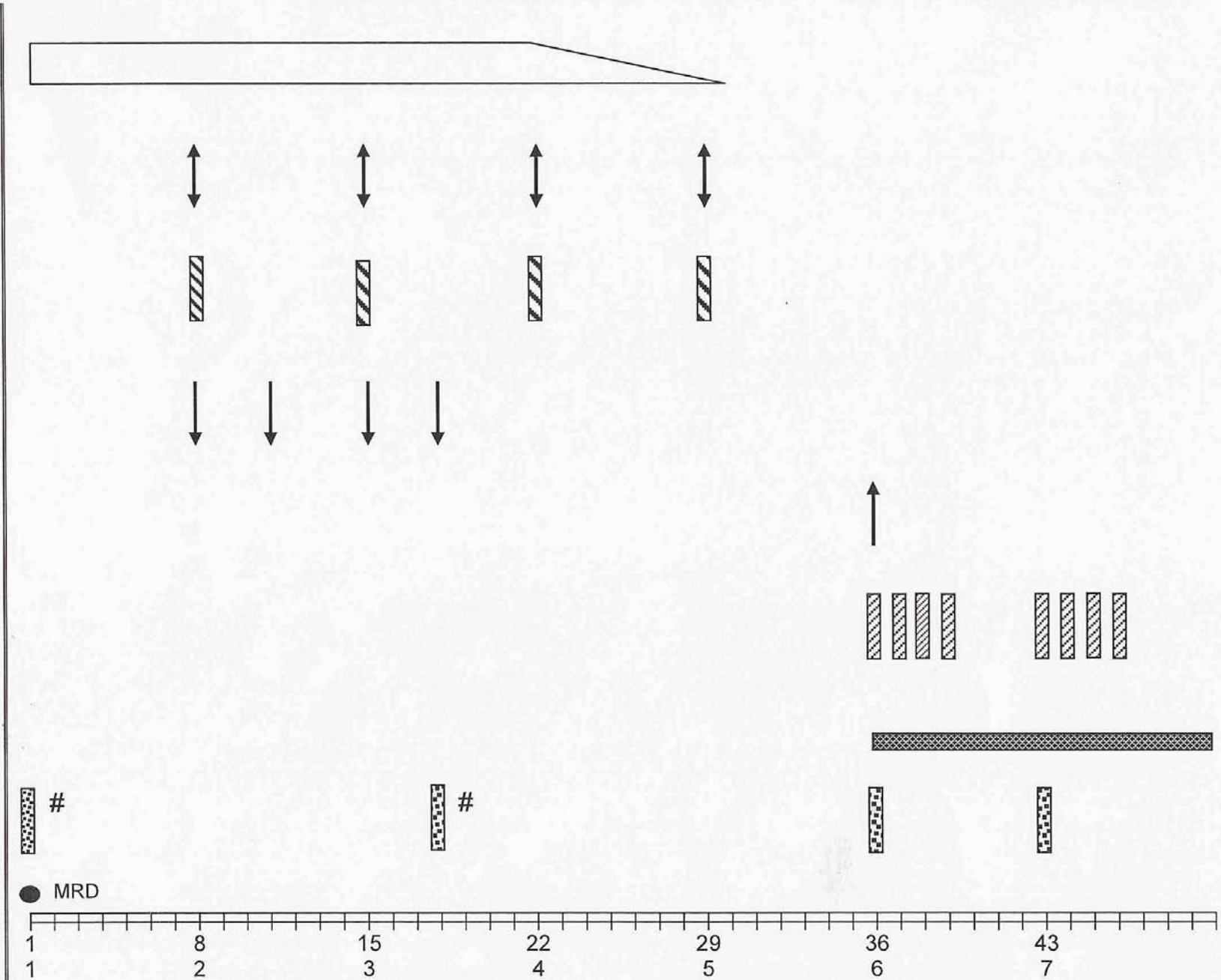
CPA  
IV 1 hr  
1,000mg/m<sup>2</sup>

ARA-C  
IV / SC  
75mg/m<sup>2</sup>

6-TG  
PO  
60mg/m<sup>2</sup>

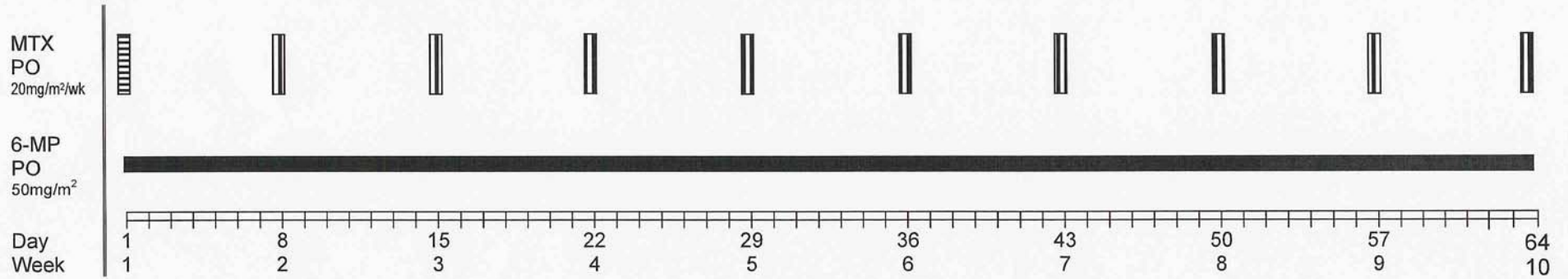
IT MTX  
Age-adjusted  
doses

BONE MARROW ● MRD



IT MTX Age-adjusted doses: 1y:8mg/ 2y:10mg/ >=3y:12mg # If CNS disease at diagnosis.

**FIGURE 13: MAINTENANCE**



Therapy management according to:	Count reading	% of dose MP/ MTX
White cell count	< 1.0 x 10 <sup>9</sup> /L	0
	1.0 - 2.0 x 10 <sup>9</sup> /L	50
	2.0 - 3.0 x 10 <sup>9</sup> /L	100
	>3.0 x 10 <sup>9</sup> /L	to 150
Lymphocytes	< 0.3 x 10 <sup>9</sup> /L	50

# Tolerance of chemotherapy

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- Influenced by several enzymes with genetic polymorphisms
  - Thiopurine S-methyl transferase (TPMT)
  - Methylenetetrahydrofolate reductase (MTHFR)
- Highly variable clinical response
  - Haematological recovery at the end of consolidation
  - Clearance of HD-MTX
  - Myelosuppression from anti-metabolites in maintenance
  - Impact on prognosis

# Purpose of the study

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- To evaluate whether myelosuppression during consolidation treatment or high-dose methotrexate clearance predicts subsequent tolerance of initial maintenance chemotherapy

# Methods

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- Children (aged 1 to 13 years) with ALL (n=13) or T-NHL (n=1), treated according to the ANZCHOG Study 8 protocol at the Mater Children's Hospital were studied retrospectively.
- Initial Maintenance Tolerance (IMT) was assessed by first white cell count (WCC) and the first dose adjustment of 6-MP and MTX in maintenance.
- Delay in administering the second dose of cyclophosphamide at the end of consolidation was used as a surrogate marker of tolerance to 6-MP given during consolidation.

## Methods (2)

- Serum MTX levels taken as per protocol at Hr 24, 36, 42, 48, 54....post dose until serum MTX level  $< 0.25\mu\text{mol/L}$
- Serum MTX clearance was calculated after each dose using nonlinear mixed-effects modelling (NONMEM) software. A further 2 children were included in MTX clearance analysis.
- NONMEM software facilitates analysis of PK data where the population is the experimental unit (not the individual)
- NONMEM is useful when there is sparse data and unbalanced dosage and blood sampling

# Results

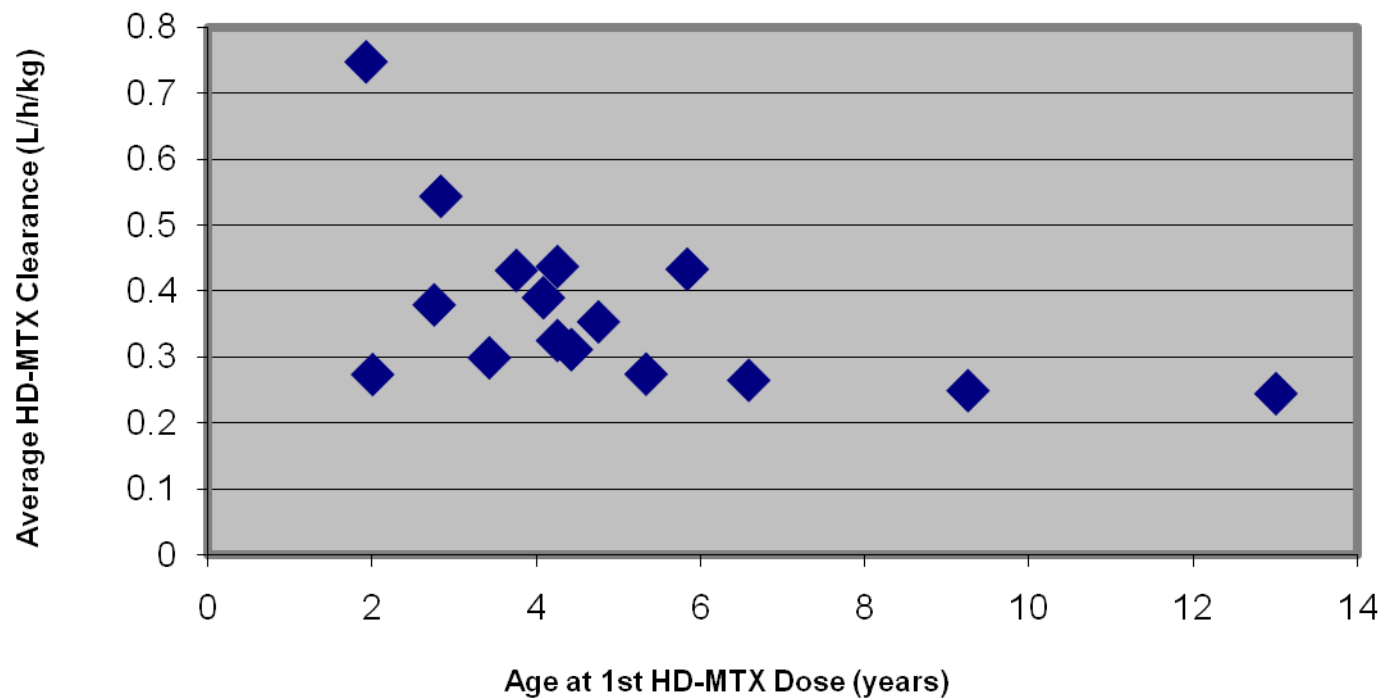
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- There was no significant correlation between MTX clearance and IMT.
- There was an inverse correlation between age and MTX clearance ( $r = -0.5218$ ,  $p = 0.04$ ).
- The only significant variation in MTX clearance occurred between the last two doses (mean difference = 0.022 L/h/kg, SD 0.035,  $p = 0.02$ ).

# Age vs HD-MTX Clearance

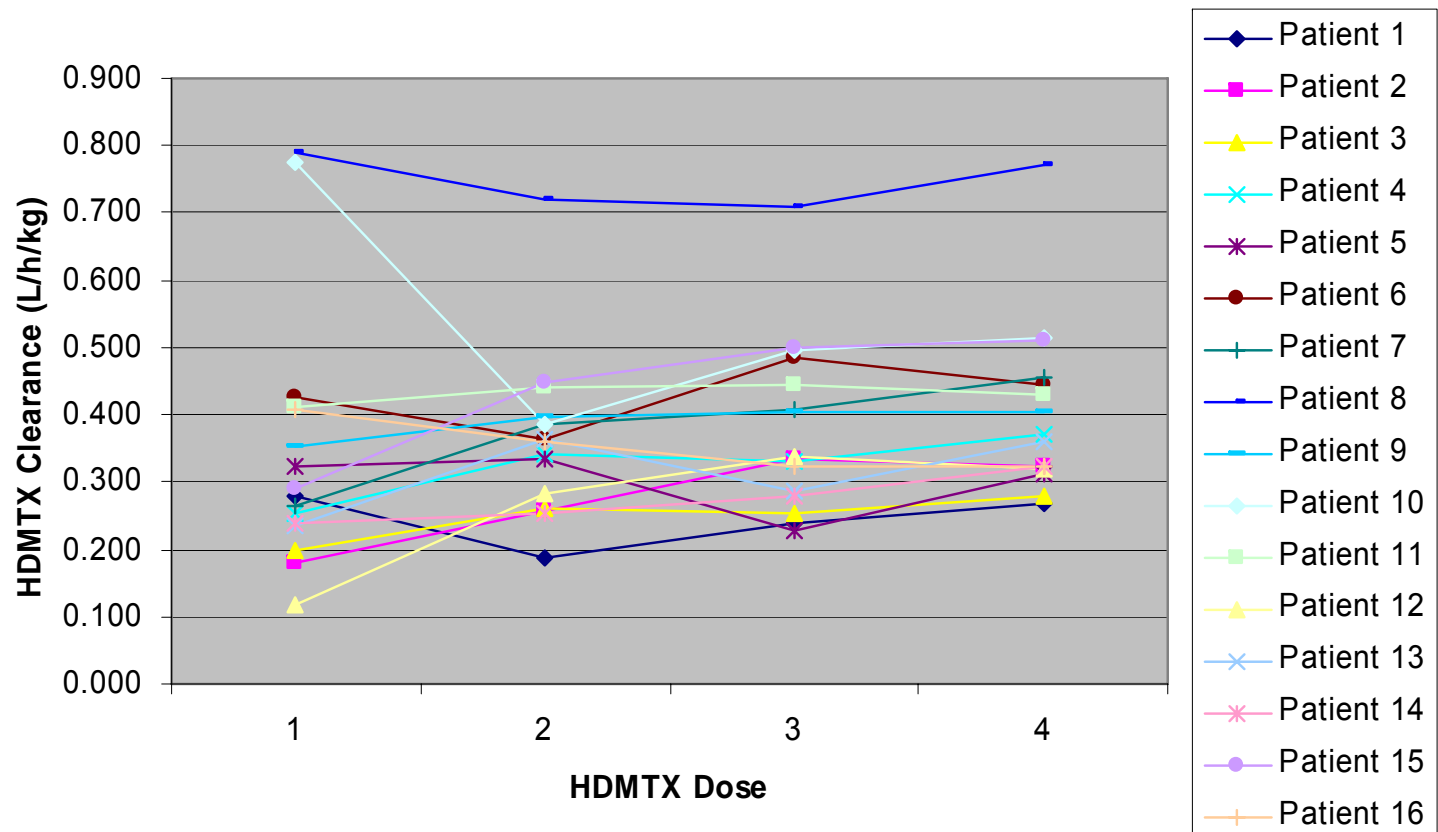
( $r = -0.5218$ ,  $p = 0.04$ )

Figure 3. Age vs Average HD-MTX Clearance



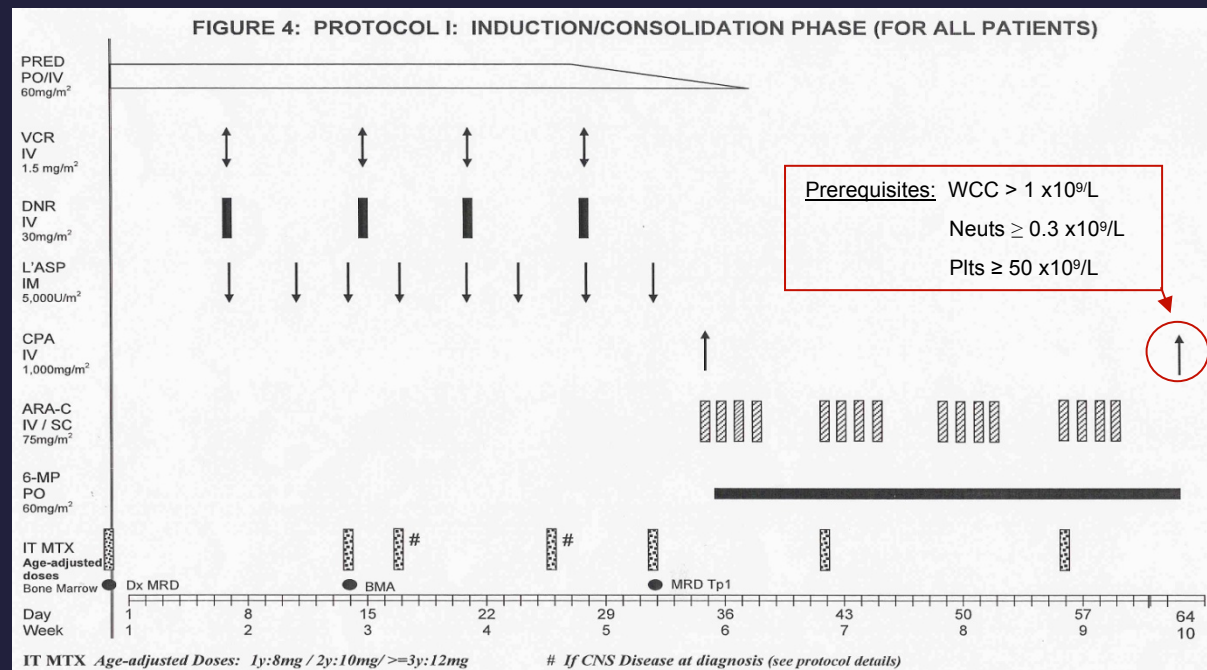
Different clearance from dose 3 to 4  
(mean difference = 0.022 L/h/kg, SD 0.035,  $p = 0.02$ )

Figure 4. HDMTX Clearance Profiles



# Results (cont.)

- Length of delay in administering the second dose of cyclophosphamide at the end of consolidation inversely correlated with the first dose adjustment of maintenance 6-MP and MTX ( $r = -0.60$ ,  $p = 0.03$ ).



## Results (cont.)

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- Length of delay in administering the second dose of consolidation cyclophosphamide did not correlate with HD-MTX clearance, nor first WCC in maintenance.

# Conclusions

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- Slower elimination of HD-MTX does not appear to adversely influence IMT.
- Delayed haematological recovery at the end of consolidation, prior to administration of HD-MTX, is a more accurate predictor of likely 6-MP intolerance.
- Assessing patient recovery from consolidation 6-MP, together with TPMT activity and genotype, may permit individualised starting doses of maintenance 6-MP and MTX.
- This could avoid the excessive myelosuppression or inadequate treatment currently seen by starting every patient at 100% of the protocol dose.

# Acknowledgements

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- **Bruce Charles**, School of Pharmacy, The University of Queensland
- **Catherine Wilkinson**, Mater Pharmacy Services
- **Steven Weier**, Mater Pathology
- **Ross Pinkerton**, Director, Queensland Children's Cancer Centre, RCH Brisbane
- **Allan Chang**, Mater Research Support Centre