TPOG - NHL 98

PROTOCOLS OF NON-HODGKIN’S LYMPHOMA

FOR

CHILDHOOD CANCER FOUNDATION

OF R.O.C.

BY

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TPOG 98 NHL protocols for Childhood Non-Hodgkin’s Lymphomas

I. 目的:
提昇國內兒童 non-Hodgkin’s lymphoma (NHL) 之治療成績。遵照兒童 NHL 治療原則：針對不同之 histology (或 immunophenotype) 及 stage，給與不同之治療方案，以期達到最好的療效及最少的毒性。

II. 背景:
TPOG-NHL92 protocols 自 1992 年推出，用於治療國內兒童 NHL，至今己六年，六年之 event-free survival (EFS) 約 65%，與歐美的成績比較，尚有一段差距。據 1997 年在 Istanbul 舉行的 SIOP (主題為 childhood lymphoma) 會中歐美各大兒癌中心，包括一些跨國的聯合治療計劃，所發表的治療成果看來：T-lymphoblastic lymphoma (LBL, mainly advanced-stage diseases) 在美國 POG，法國 SFOP 的 3-5 years EFS 約為七成左右，而德國的 BFM 86/90 for T-LBL，治療成績更高達近八、九成。TPOG 92LB for lymphoblastic lymphoma 是依據 POG T3 protocol 製定的，成績尚可；如果我們改用 BFM 來治療 T-LBL；則可與目前 TPOG 97VHR (同源於 BFM-ALL protocol) for T-cell ALL，對治療 T-cell diseases 有連貫性。

對 B-cell lymphoma 及 B-cell ALL 之治療，法國 SFOP LMB89 對 stage I, II lymphoma 之 3-year EFS 達 96%，stage III 93%，stage IV & B-cell ALL 88%，initial CNS (+) 79%；而德國 NHL- BFM 90 對各種 B-cell diseases 的治療成果也多在九成上下。TPOG 92SNC protocol 是依據 SFOP LMB89 protocol 製定的，現在如果換 BFM 試試看，也是不錯的想法。另外，BFM 之 B-NHL protocol 更被德國及歐卅多國用來治療兒童之 anaplastic large cell lymphoma (ALCL)，成績多在近八成上下之 EFS，比法國 SFOP HM89/91 for ALCL 的成績好 (3 year EFS 60%)；且不用另外的 protocol。大家都感覺近來 ALCL 佔兒童 NHL 的比例愈來愈高，可高達 10-15%，佔兒童 large cell lymphoma 的一半。兒童 large cell lymphoma 的治療，先前一直沒有很確定的方案；如果採用 BFM 之 B-NHL protocol 來治療所有 B-cell diseases 及 ALCL，就解決大部份的兒童 non-lymphoblastic lymphomas 了。

III. Patient Eligibility:
All previously untreated patients ☐ 18 years of age, diagnosed with any form of NHL or B-cell acute lymphoblastic leukemia (ALL) will be eligible. (lymphoblastic lymphoma with ☐ 25% blasts in the marrow is defined as having non B-cell ALL and treated elsewhere accordingly)

IV. Pretreatment Evaluation:
Standard Staging Procedures

History and physical examination
Complete blood count
Liver and renal serum chemistries include serum LDH and uric acid
Bone marrow examination (aspiration / biopsy)
Cerebrospinal fluid examination
Cytochemical and immunological evaluation of ascites or pleural fluid
Chest x-ray
Chest CT scan (if chest x-ray findings are abnormal or suspiciously abnormal)
Abdominal ultrasound examination (include liver/spleen, kidneys, abdomen and pelvis)
Abdominal CT scan (can be waived if ultrasound is adequate)
Head and neck CT scan or MRI (for head and neck primaries)
Bone scan
Gallium scan (optional, preferred in bone disease)
Dental evaluation in patients with Burkitt’s lymphoma

V. Staging
According to the St. Jude staging system with one modification:
Patients with multifocal bone involvement will be classified as stage IV.

Stage I
A single tumor (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen.

Stage II
A single tumor (extranodal) with regional node involvement.
Two or more nodal areas on the same side of the diaphragm.
Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm.
A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable.

Stage III
Two single tumors (extranodal) on opposite sides of the diaphragm.
Two or more nodal areas above and below the diaphragm.
Any primary intrathoracic tumor (mediastinal, pleural, or thymic).
Extensive primary intraabdominal disease.
Any paraspinal or epidural tumor, whether or not other sites are involved.

Stage IV
Any of the above with initial involvement of the central nervous system, bone marrow, or both.
Multifocal bone involvement.
VI. Stratification of Treatment by NHL Subtypes

**TPOG 98 T-LBL**  (based on ALL-BFM 86/90 protocols)

**Patient Eligibility:**
- Lymphoblastic lymphoma (T-cell or precursor B-cell type)
- Immunoblastic lymphoma of T-cell lineage
- Other Peripheral T-cell lymphomas
- Cases that are not further classifiable by means of histology and/or cytology will be included in this group if T-lineage antigens are expressed. If the immunophenotype is not available, cases of mediastinal localization will be included in this group as well.

**Treatment Plan:** as depicted in the schema and table (on the following pages)
- Arm a (TPOG 98 T-LBL a) for Stage I and Stage II cases
- Arm b (TPOG 98 T-LBL b) for Stage III and Stage IV cases

**Special Notes:**
- Before, during and 24 hours after the infusion of HD-MTX, hydration with alkalinized isotonic fluid should be given and be sure of having adequate renal function. Serum MTX level should be measured at 48 hours after starting MTX infusion. If the MTX level is $<0.5 \mu M$ at hr 48, leucovorin will be given as scheduled (15mg/m² q6h, starting at hr 36 for 6 doses, iv for the first dose, and iv/po for the rest doses); if the MTX level is $\geq 0.5 \mu M$ at hr 48, it should be monitored daily and leucovorin dose should be increased and extended till the MTX level falls $<0.1 \mu M$.
- Cranial irradiation for patients of stage III and IV will be performed during the second phase of reinduction protocol II. The dosage is 12 Gy for all CNS-negative patients. For patients with overt CNS disease, the dosage will be 18 Gy in the second year of life and 24 Gy in older children. Children less than 1 year of age do not receive cranial radiotherapy, even with overt CNS disease. In males with testicular involvement, irradiation (24 Gy) of the testes will be performed.
- Patients with a persistent tumor after induction protocol I may receive either local radiotherapy (30 Gy) or surgical resection.

**TPOG 98 B-NHL**  (based on NHL-BFM 86/90 protocols)

**Patient Eligibility:**
- Burkitt’s or Burkitt’s-like lymphoma
- Diffuse large B-cell lymphoma (large cleaved cell, large non-cleaved cell, mixed small and large cell lymphoma)
- Primary mediastinal large B-cell lymphoma
- B-cell ALL
- CD30+ (Ki-1) anaplastic large cell lymphoma (ALCL), irrespective of immunologic lineage
Cases that are not further classifiable by means of histology and/or cytology will be included in this group if B-lineage antigens are expressed. If the immunophenotype is not available, cases of abdominal localization will be included in this group as well.

**Treatment Plan:** as depicted in the schema and table (on the following pages)

- Patients will be further stratified according to the risk criteria and treated accordingly
- Arms R1, R2, R3 for non-ALCL B-cell diseases in corresponding risk groups.
- Arms K1, K2, K3 for ALCL cases in corresponding risk groups.

**Special Notes:**

- Patients with advanced stage Burkitt’s lymphoma or B-cell ALL are at greatest risk for developing acute tumor lysis syndrome. Intensive supportive care to prevent this serious complication is mandatory, and should follow the guidelines as follows:

<table>
<thead>
<tr>
<th>Modality</th>
<th>Guidelines</th>
</tr>
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<tbody>
<tr>
<td>Hydration</td>
<td>5% glucose 0.25NS at 2-4 times maintenance requirement, to maintain urine output ≥ 100ml/m²/hr, and urine specific gravity ≤ 1.010</td>
</tr>
<tr>
<td>Alkalization</td>
<td>50-100 mEq/L NaHCO₃, to maintain urine pH 7.0-7.5</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>10mg/kg/day PO</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.5-1.0 g/kg can be used if patient has oliguria unresponsive to increased hydration</td>
</tr>
<tr>
<td>Monitor</td>
<td>Na⁺, K⁺, Cl⁻, CO₂, Ca²⁺, PO₄, uric acid, BUN, creatinine q6h Urine output, pH, specific gravity Cardiac monitoring if there is hyperkalemia or hypocalcemia Respiratory and CNS monitoring</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>To be started when patient is stabilized and has adequate urine output</td>
</tr>
<tr>
<td>Dialysis</td>
<td>To be used for progressive renal failure with K&gt;6 mEq/L, P&gt;10mg/dl, oliguria, anuria, and volume overload unresponsive to the above measure</td>
</tr>
</tbody>
</table>

- Guidelines for HD-MTX administration and following leucovorin rescue are the same as those for the TPOG 98 T-LBL protocol.

- Conditions for starting a course of therapy will be as follows: platelet count >50,000/μL, WBC count>1,000/μL and ANC>200/μL for courses 2, 3 and 4, and WBC>2,000/μL and ANC>500 for courses 5 and 6. The minimal interval between the first day of two successive courses is 2 weeks.

- Patients of risk groups R2 and R3 with incomplete response after 2 courses (AA-BB) will receive an intensified course CC. After this course, patients with no residual or necrotic residual tumor will receive 3 more therapy courses: AA-BB-CC; patients with viable tumor will be candidates for autologous BMT.
Cranial radiotherapy (24 Gy) given after completion of 6 courses of chemotherapy is optional for patients with overt CNS disease. Patients without CNS disease do not receive cranial irradiation. Another option for CNS-positive patients will be intraventricular applied therapy. The systematic chemotherapy is according to the K3 arm schedule (AA-BB-CC-AA-BB-CC). The CNS therapy will be as follows: intrathecal triple medication (TIT) given via lumbar puncture on day 1 and on the first day of the first course AA. During courses 2-6, MTX 3mg (also adjusted for age <3) and hydrocortisone 3mg given intraventricularly via Ommaya reservoir on 4 consecutive days (d1-4) followed by one dose of Ara-C (30mg) on day 5. No radiation therapy will be used.

VI. Response Criteria

- In TPOG 98 T-LBL group, tumor response will be evaluated at day 42 and at the end of induction protocol I. Subsequent evaluation is performed at the beginning of reinduction protocol II, and at 1-2 month intervals thereafter until the end of maintenance therapy.
- In TPOG 98 B-NHL group, tumor response will be evaluated after the first two therapy courses, and subsequent evaluation is performed at the beginning of every therapy course, later in 4-week intervals during the first year and in 2-month intervals during the second year.
- Complete response is defined as disappearance of lymphoma cells in BM or CSF, or complete regression of local tumor proved by imaging studies or second-look surgery.
- Initial tumor failure is defined as persistence of lymphoblasts in the BM and/or CSF and/or as incomplete regression of local tumor followed by progression during chemotherapy.
- Relapse is defined as recurrence of lymphoma at any site after complete disappearance of lymphoblasts from the blood, CSF, and BM, as well as disappearance of all tumor mass on clinical examination, imaging methods (ultrasonography, x-ray, CT, or MRI), or second-look surgery.

VII. REFERENCES


**TPOG 98 T-LBL Protocol**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days when administration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone (orally)</td>
<td>60 mg/m²</td>
<td>1-28</td>
</tr>
</tbody>
</table>
Vincristine (IV bolus) 1.5 mg/m² (max 2mg) 8, 15, 22, 29
Epirubicin (1-hr iv infusion) 20 mg/m² 8, 15, 22, 29
Asparaginase (IM) 5,000 IU/m² 15,17,19,22,24,26,29,31
Cyclophosphamide (1-hr ivf) 1,000 mg/m² 36, 64
Cytarabine (IV/SC) 75 mg/m² 38-41,45-48,52-55,59-62
Mercaptopurine (orally) 60 mg/m² 36-63
TIT (MTX, HC, AraC) (12, 12, 24 mg) 1, 22, 45, 59

Consolidation protocol M
Mercaptopurine 25 mg/m² 1-49
MTX (24-hour infusion) 5 gm/m² 1, 15, 29, 43
with CF rescue 15 mg/m² q6h x 6 or more (starts from hr36)
TIT (MTX, HC, AraC) (12, 12, 24 mg) 1, 15, 29, 43

Reinduction protocol II
Dexamethasone (orally) 10 mg/m² 1-21
Vincristine (IV bolus) 1.5 mg/m² (max 2mg) 8, 15, 22, 29
Epirubicin (1-hr iv infusion) 30 mg/m² 8, 15, 22, 29
Asparaginase (IM) 5,000 IU/m² 8, 11, 15, 18
Cyclophosphamide (1-hr ivf) 1,000 mg/m² 36
Cytarabine (IV/SC) 75 mg/m² 38-41, 45-48
Thioguanine (orally) 60 mg/m² 36-49
TIT (MTX, HC, AraC) (12, 12, 24 mg) 38, 45

Maintenance therapy (until 2 years from start of treatment)
6-MP 50 mg/m² p.o. daily and MTX 20 mg/m² p.o. weekly; pulses every 9 weeks with
Vincristine 1.5 mg/m² i.v. d 57, 63 & Dexan 6 mg/m² p.o. d 57-63, q9w x 6

* Adjustment of time schedule can be made for clinical condition and marrow recovery
¢ HD-MTX 24-hour infusion: 10% of the dose iv infusion over 30 minutes, and then 90% as
a 23.5-hour continuous iv infusion, CF rescue starts at hr 36 after starting MTX infusion.
MTX level should be measured at hr48, if \( \geq 0.5 \) M, measured daily and increase and extend
leucovorin dose till MTX level < 0.1 M.
§ TIT dose adjusted for age<3 (TIT given at 8-12 hours before starting 24-hour HD-MTX)

<table>
<thead>
<tr>
<th>TIT</th>
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<th>1-2yr</th>
<th>2-3yr</th>
<th>&gt;3yr</th>
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<tbody>
<tr>
<td>MTX</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>HC</td>
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<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>AraC</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

£ Additional doses of TIT at days 8, 15, 29 for CNS-positive patients
### TPOG 98 B-NHL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days when administration</th>
</tr>
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<tbody>
<tr>
<td><strong>Cytoreductive prephase</strong></td>
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<td></td>
</tr>
<tr>
<td>Prednisolone (orally/IV)</td>
<td>30 mg/m²</td>
<td>1-5</td>
</tr>
<tr>
<td>Cyclophosphamide (IV)</td>
<td>200 mg/m²</td>
<td>1-5</td>
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<tr>
<td><strong>Course A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone (orally)</td>
<td>10 mg/m²</td>
<td>1-5</td>
</tr>
<tr>
<td>Ifosfamide (1-hour infusion)</td>
<td>800 mg/m²</td>
<td>1-5</td>
</tr>
<tr>
<td>MTX (24-hour infusion)</td>
<td>500 mg/m²</td>
<td>1</td>
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<tr>
<td>TIT (MTX, HC, AraC)</td>
<td>(12, 12, 24 mg)</td>
<td>1</td>
</tr>
<tr>
<td>Cytarabine (1-hour infusion)</td>
<td>150 mg/m²</td>
<td>q12h</td>
</tr>
<tr>
<td>Etoposide (1-hour infusion)</td>
<td>100 mg/m²</td>
<td>4,5</td>
</tr>
<tr>
<td><strong>Course B</strong></td>
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<tr>
<td>Prednisolone (orally)</td>
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<td>TIT (MTX, HC, AraC)</td>
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<td>Epirubicin (1-hour infusion)</td>
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<tr>
<td><strong>Course AA</strong></td>
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</tr>
<tr>
<td>Vincristine (IV)</td>
<td>1.5 mg/m²</td>
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<tr>
<td>MTX (24-hour infusion)</td>
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<tr>
<td><strong>Course BB</strong></td>
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<tr>
<td>Vincristine (IV)</td>
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<td><strong>Course CC</strong></td>
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<td>TIT (MTX, HC, AraC)</td>
<td>(12, 12, 24 mg)</td>
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* MTX 24-hour infusion: 10% of the dose iv infusion over 30 minutes, and then 90% as a 23.5-hour continuous iv infusion. in courses A & B, leucovorin 15 mg/m² iv starts at hr 48 after starting MTX infusion q3h for 3 times. In courses AA & BB, leucovorin starts at hr 36, q6h x 6 or more; measure MTX level at hr 48, if ≥ 0.5 M, measure it daily, and increase and extend leucovorin dose till MTX level < 0.1 M.

* I. Vent via Ommaya reservoir for CNS disease, MTX& HC on d1-4, AraC on d5 of K3 courses 2-6

<table>
<thead>
<tr>
<th>TIT</th>
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<table>
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<td>HC</td>
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<td>AraC</td>
<td>15</td>
<td>20</td>
<td>25</td>
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</table>

* TIT & intraventricular dose adjusted for age<3 (in A & B, TIT given at hour 2 after starting 24-hr MTX infusion; in AA & BB, TIT given at 8-12 hours before starting 24-hr HDMTX infusion)
**TPOG 98 T-LBL** Protocol for Childhood Lymphoblastic Lymphoma (T-cell, Precursor-B cell type), Immunoblastic T, and Peripheral T-cell lymphoma

**Arm a : Stage I, II**
- I
- M
- Maintenance

**Arm b : Stage III, IV**
- I
- M
- II
- CRT

**Induction (Protocol I, 9w+1d)**
- PRED 60mg/m²/d PO decreasing
- VCR 1.5mg/m² iv
- EPR 20mg/m² 1hr ivf
- L-ASP 5,000 U/m² im
- CP 1000mg/m² 1hr ivf
- Ara-C 75mg/m² iv/sc
- 6-MP 60mg/m²/d PO
- TIT* (MTX/HC/AraC)

**Consolidation (Protocol M, 7w)**
- 6-MP 25mg/m²/d PO
- HD-MTX 5g/m² 24hr ivf
- CF rescue 15mg/m²
- TIT*

**Reinduction (Protocol II, 7w)**
- Dexan 10mg/m²/d PO decreasing
- VCR 1.5mg/m² iv
- EPR 30mg/m² 1hr ivf
- L-ASP 5,000 U/m² im
- CP 1000mg/m² 1hr ivf
- Ara-C 75mg/m² iv/sc
- 6-TG 60mg/m²/d PO
- TIT*

**Maintenance (until 2 years from start of treatment)**
- 6-MP 50mg/m²/day PO and MTX 20mg/m²/wk PO
- Vincristine 1.5mg/m² iv days 57,63 &
- Dexan 6mg/m²/d PO days 57-63, pulses q9w x 6

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<table>
<thead>
<tr>
<th>TIT</th>
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<td>AraC</td>
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</table>

* CRT: Cranial irradiation
  - 12Gy for CNS prophylaxis
  - 24Gy for CNS disease
  - additional TIT for CNS disease only

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* MTX 6 8 10 12
  * HC 6 8 10 12
  * AraC 12 16 20 24
TPOG 98 B-NHL Protocols for Childhood B-cell Lymphomas (Burkitt’s, Burkitt’s-like, diffuse large B-cell, primary mediastinal large B-cell lymphoma), B-cell ALL, and anaplastic large cell lymphoma (ALCL)

**Risk Grouping**

<table>
<thead>
<tr>
<th>Risk Grouping</th>
<th>Risk grouping for ALCL</th>
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<tbody>
<tr>
<td>R1: Completely resected</td>
<td>K1: Stage (St Jude) I, and Stage II-completely resected</td>
</tr>
<tr>
<td>R2: Unresected, extraabdominal only, or abdominal tumor and LDH&lt;500 U/L</td>
<td>K2: Stage II-not resected, and stage III</td>
</tr>
<tr>
<td>R3: Abdominal primary and LDH&gt;500 U/L or BM+ or/and CNS+, B-cell ALL, or with multifocal bone disease</td>
<td>K3: Stage IV or multifocal bone disease</td>
</tr>
</tbody>
</table>

**AA**

1. **VCR 1.5mg/m² iv**
2. **TIT (MTX,HC,AraC)**
3. **HD-MTX 5g/m² 24hr ivf,CF**
4. **IFO 800mg/m² 1hr ivf**
5. **Dexan 10mg/m²/d PO**

1 2 3 4 5 days

**BB**

1. **VCR 1.5mg/m² iv**
2. **TIT (MTX,HC,AraC)**
3. **HD-MTX 5g/m² 24hr ivf,CF**
4. **CP 200mg/m² 1hr ivf**
5. **Dexan 10mg/m²/d PO**

1 2 3 4 5 days

**CC**

1. **VCR 1.5mg/m² iv**
2. **TIT (MTX,HC,AraC)**
3. **VP-16 150mg/m² 1hr ivf**
4. **Dexan 20mg/m²/d PO**

1 2 3 4 5 days

*Incomplete response

**Autologus BMT**

**Pred 30mg/m² PO**

1 2 3 4 5 days

**CP 200**

1 2 3 4 5 days

A same as AA, B same as BB, except:
1. omit VCR
2. MTX 0.5g/m² 24hr ivf

ID or HD-MTX 24hr ivf: 10% of the MTX dose iv over 30', then 90% as a 23.5hr continuous iv infusion

CF rescue: 15mg/m² iv q6h
start from hr36 for ≥6 doses for AA & BB;
q3h start from hr48 for 3 doses for A & B

**TIT <1y 1-2y 2-3y >3y**

<table>
<thead>
<tr>
<th>MTX</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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<tbody>
<tr>
<td>HC</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>AraC</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

* CNS disease: Cranial R/T 2.4Gy after R3; or I. Vent. Via Ommaya (MTX d1-4, AraC d5, courses 2-6 of K3)