A	REGIMEN NAME	Hyper-CVAD Chemotherapy

Cancer	Non-Hodgkin's Lymphoma (High Grade) Lymphoblastic Lymphoma	Curative
Regimen Category	Core: Standard therapy endorsed by the Disease Site Group and a regimen widely used by most Integrated Cancer Programs in this disease site	

B DRUG REGIMEN

Course A:

CYCLOPHOSPHAMIDE	300mg/m^2	IV over 3 hours	Q12H x 6 doses Days 1, 2, and 3

MESNA may be given as an uroprotectant at the same total dose as cyclophosphamide but given by continuous infusion starting with cyclophosphamide and ending 6 hours after the last dose. (Although Mesna is recommended in the cited reference (Kantarjian et al.), most RCC's usually do not administer Mesna with this dose of Cyclophosphamide.)

METHOTREXATE	12mg	IT	Day 2
DOXORUBICIN	50mg/ m^2	IV	Day 4
VINCRISTINE	2mg	IV	Days 4 and 11
DEXAMETHASONE	40mg/day	IV or PO	Days 1 to 4 Days 11-14
CYTARABINE	70mg	IT	Day 7

Course B:

METHOTREXATE	1000mg/ m^2	IV over 24 hours	Day 1
LEUCOVORIN	25mg/ m^2	IV 24 hours after starting Methotrexate infusion	Q6H X 6 doses
Sodium Bicarbonate	600mg	PO (starting day before Methotrexate)	TID X 4 Days
CYTARABINE	3000mg/ m^2	IV over 2 hours	Q12H X 4 doses Days 2 and 3

C CYCLE FREQUENCY

A total of 8 cycles is administered (4 X A, 4 X B) with the goal to give treatment as rapidly as possible.

D PREMEDICATION AND SUPPORTIVE MEASURES

ANTIEMETIC REGIMENS:
HESKETH LEVEL 5

- *With high dose Methotrexate, give hydration with Sodium Bicarbonate for 48 hours.*
- *Prophylactic use of Dexamethasone 0.1% or Pred Forte Ophthalmic solution 1-2 drops q4h while awake for 7 days (during high dose Cytarabine) to prevent conjunctivitis*
- *Antibiotic prophylaxis may be given (see reference)*

E DOSE MODIFICATION

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Hematologic Toxicities
See **Appendix 6** for general recommendations.
G-CSF support should be considered after first episode of febrile neutropenia or delay of dose > or = 1 week.

Renal Dysfunction

Creatinine Clearance	
0.2-0.8mL/sec	**REDUCE** Methotrexate to ***50%*** dose
<0.2mL/sec	**OMIT** dose of Methotrexate

There is no consistent evidence indicating a need for Cyclophosphamide dosage modification in patient with renal impairment. Dosage may be halved or interval increased by 50-100% if CrCl <0.3 mL/second.

If there is evidence of renal insufficiency (↑ Serum Creatinine / ↓ Creatinine Clearance), consider alternate therapy (Cerebellar toxicity with high-dose Cytarabine associated with reduced renal clearance).

E DOSE MODIFICATION (cont.)

Hepatic Dysfunction

Bilirubin (µmol/L)	*% usual dose*
1-2X ULN	**REDUCE** Vincristine to ***50%*** dose, and **REDUCE** Doxorubicin to ***50%*** dose
2-4X ULN	**REDUCE** Vincristine to ***25%*** dose, and **REDUCE** Doxorubicin to ***25%*** dose
2-3X ULN	**REDUCE** Methotrexate to ***75%*** dose
>3X ULN	**OMIT** Methotrexate dose
>4X ULN	**OMIT** Doxorubicin dose

Neurotoxicity

Symptom	*% usual dose of Vincristine*
1. areflexia only	100%
2. abnormal buttoning, writing	67%
3. moderate motor neuropathy (± cranial)	Hold until recovery then reduce dose by 50%
4. severe motor neuropathy	Omit

F ADVERSE EFFECTS

Refer to Cyclophosphamide, (Mesna), Doxorubicin, Vincristine, Dexamethasone, Methotrexate, Cytarabine, and Leucovorin drug monograph for full details of adverse effects.

Most Frequently Occurring Adverse Effects

- Myelosuppression
- Hyperuricemia
- Stomatitis
- Nausea and vomiting
- Neurotoxicity
- Stomatitis
- Vesicant
- Cardiotoxicity
- Hyperglycemia
- Gastric irritation
- Hemorrhagic cystitis
- Alopecia
- Insomnia
- Constipation
- Acute encephalopathy
- Pulmonary toxicity
- Pigmentation discorder
- Diarrhea
- Infertility
- Hepatotoxicity
- Fever
- Cerebellar toxicity
- Conjunctivitis
- Flu like syndrome
- Typhlitis and necrotising colitis

G INTERACTIONS

Refer to Cyclophosphamide, (Mesna), Doxorubicin, Vincristine, Dexamethasone, Metho trexate, Cytarabine, and Leucovorin drug monograph for full details.

H ADMINISTRATIVE INFORMATION AND SPECIAL PRECAUTIONS

Refer to Cyclophosphamide, (Mesna), Doxorubicin, Vincristine, Dexamethasone, Methotrexate, Cytarabine, and Leucovorin drug monograph for full details.

I CLINICAL MONITORING

- Clinical toxicity assessment (including cardiotoxicity, gastrointestinal, neurotoxicity, cerebellar toxicity, sensory, local, cystitis and stomatitis).
- Routine blood glucose test.
- Baseline and regular cardiac examination for patients with cardiac risk factors (including prior therapy with Daunorubicin, Epirubicin, Mitoxantrone, or other cardiotoxic drug) and cumulative Doxorubicin doses > 450mg/m^2.
- CBC before each cycle. Interim counts should be done in first cycle and repeated if dose modifications necessary.
- Baseline and regular liver and renal function tests.
- Baseline and periodic pulmonary examination.
- Baseline and regular ophthalmic examination.

J ADMINISTRATION INFORMATION

Patient visit	Should be administered in hospital
Approximate drug cost (chemotherapy only)	$ 145.00 per Block A treatment cycle $ 685.00 per Block B treatment cycle

Complexity Value*

BLOCK A

Regimen	200 Per cycle (value normalized to 28 days)
Pharmacy	68 Per cycle
Chemo Nursing	132 Per cycle

BLOCK B

Regimen	97 Per cycle (value normalized to 28 days)
Pharmacy	39 Per cycle
Chemo Nursing	58 Per cycle

* Complexity value is the fixed time spent in minutes by nursing and pharmacy with respect to administration for each treatment cycle.

K KEY REFERENCE(S)

Kantarjian HM, O'Brien S. Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol. 2000 Feb; 18(3): 547-61.

L OTHER NOTES

This regimen should only be given by hematologists trained in the care of high grade lymphoma patients, and practicing in institutions with adequate acute care designed to support high grade lymphoma patients.

For the treatment of Lymphoblastic Lymphoma, hematologists may refer to Acute Lymphocytic Leukemia regimens (i.e. Dana Farber).