A	REGIMEN NAME	MAGRATH PROTOCOL Chemotherapy

Cancer	Lymphoblastic Lymphoma Burkitt's Lymphoma	Curative Intent
Regimen Category	Core: Standard therapy; a regimen widely used by most Regional Cancer Centres in this disease site	
Rationale and Indication	First line therapy for Burkitt's lymphoma	

B DRUG REGIMEN

Regimen A- CODOX M

CYCLOPHOSPHAMIDE (Round to nearest 10mg)	800mg/m² in 500mL NS over 1hour	IV	Day 1
CYCLOPHOSPHAMIDE (Round to nearest 10mg)	200mg/m² in 500mL NS over 1hour	IV	Days 2-5
DOXORUBICIN (Round to nearest 1 mg)	40mg/m²	IV	Day 1
VINCRISTINE (Round to nearest 0.1 mg)	1.5mg/m² (Max 2mg)	IV	Days 1, and 8 (also day 15 in cycle 3)
CYTARABINE	70mg	IT	Days 1, 3
METHOTREXATE (MTX) (Round to nearest 12.5mg)	1200mg/m² in 1L NS over 1 hour	IV	Day 10
METHOTREXATE (Round to nearest 12.5mg)	240mg/m²/hr in 1L NS over 23 hrs	CIV	Day 10 (after MTX 1 hour infusion)
LEUCOVORIN (Round to nearest 1mg)	192mg/m²	IV	Day 11 (12 hrs post completion of MTX CIV infusion)
LEUCOVORIN (Round to nearest 1mg)	12mg/m²	IV	Day 11 (6 hrs post loading dose) Q6H until MTX level is < 0.1 umol

B DRUG REGIMEN (CONT.)

FILGRASTIM	7.5ug/kg	SC	Starting day 13 (daily until ANC > 1.0 X 10^9/L)
METHOTREXATE	12mg	IT	Day 15

Regimen B – IVAC

IFOSFAMIDE (Round to nearest 10mg)	1500mg/m² in 500mL NS over 2 hours	IV	Days 1 to 5
MESNA (Round to nearest 1mg)	1500mg/m² in 500mL NS over 2 hours	IV	Days 1 to 5 (concurrent with Ifosfamide)
MESNA (Round to nearest 1mg)	360mg/m² in 100mL NS over 30min	IV	Days 1 to 5 (4 hrs post completion of Ifosfamide infusion, Q3H X 2 doses)
CYTARABINE (Round to nearest 10mg)	2000mg/m² in 250mL NS over 1 hr	IV	Days 1 & 2 (Q12H X 4 doses)
ETOPOSIDE (Round to nearest 10mg)	60mg/m² in 500mL NS over 1 hr	IV	Days 1 to 5
METHOTREXATE (Round to nearest 0.2mg)	12mg/m²	IT	Day 5
FILGRASTIM	7.5ug/m^2	SC	Starting day 7 (daily until ANC>1. 0 X 10^9/L)

C CYCLE FREQUENCY

ADVANCE STAGE - alternate A + B regimens every 3 weeks for total of 6 cycles
(3 cycles of A & 3 cycles of B)

LIMITED STAGE - 3 cycles of A regimen every 3 weeks

D PREMEDICATION AND SUPPORTIVE MEASURES

ANTIEMETIC REGIMENS:

Regimen A:

DAY 1 – HESKETH LEVEL 5

DAYS 2, 3 ,4 , & 10 – HESKETH LEVEL 4

DAYS 8 & 15 – HESKETH LEVEL 1

Regimen B:

DAYS 1 to 2 – HESKETH LEVEL 5

DAYS 3 to 5 – HESKETH LEVEL 4

Prophylactic coritcosteroid ophthalmic eye drops is recommended concurrently with high dose cytarabine

E DOSE MODIFICATIONS

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.

Renal Failure

Creatinine Clearance	% usual dose
0.2-0.8mL/sec	**REDUCE** Methotrexate to ***50%*** dose and **REDUCE** Etoposide to ***75%*** dose
<0.3mL/sec	**REDUCE** Cyclophosphamide to ***50%*** dose
< 0.2mL/sec	**OMIT** Methotrexate **REDUCE** Etoposide to ***50%*** dose
Serum Creatinine >200µmol/L	**REDUCE** Ifosfamide to ***75%*** dose
Serum Creatinine >300µmol/L	**REDUCE** Ifosfamide to ***67%*** dose *(Suggested action)*

E DOSE MODIFICATIONS (CONT.)

Hepatic Dysfunction

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

Consider Ifosfamide dose reduction if LFT's elevated (eg. Bilirubin or AST)
(Suggested action)

Neurotoxicity

1. Mild motor neuropathy	**REDUCE** Vincristine to ***2/3*** dose
2. Moderate motor neuropathy	**REDUCE** Vincristine to ***1/2*** dose
3. Severe motor neuropathy	**STOP** treatment with Vincristine

F ADVERSE EFFECTS

Refer to the Cyclophosphamide, Cytarabine, Methotrexate, Leucovorin, Doxorubicin, Vincristine, Ifosfamide, and Mesna monographs for full details of adverse effects.

Most frequently occurring adverse effects:

- Myelosuppression
- Hyperuricemia
- Nausea and vomiting
- Stomatitis
- Neuropathy
- Vesicant
- Cardiotoxicity
- Hemorrhagic cystitis
- Alopecia
- Cerebral dysfunction
- Acute encephalopathy (including seizures)
- Pulmonary toxicity
- Pigmentation disorder
- Conjunctivitis
- Hypotension
- Hepatotoxicity

G INTERACTIONS

Refer to the Cyclophosphamide, Cytarabine, Methotrexate, Leucovorin, Doxorubicin, Vincristine , Ifosfamide and Mesna monographs for full details.

H DRUG ADMINISTRATION AND SPECIAL PRECAUTIONS

Refer to the Cyclophosphamide, Cytarabine, Methotrexate, leucovorin, Doxorubicin, Vincristine, Ifosfamide and Mesna monographs for full details.

I CLINICAL MONITORING

- Clinical toxicity assessment (including gastrointestinal, stomatitis, local toxicity, CNS toxicity, conjunctivitis, pulmonary toxicity, cardiotoxicity, and cystitis).
- CBC before each cycle. Interim counts should be done in first cycle and repeated if dose modification necessary.
- Baseline and regular cardiac examination for patients with cardiac risk factors (including prior therapy with Epirubicin, Mitoxantrone, or other cardiotoxic drug) and cumulative doxorubicin doses > 450mg/m^2.
- Baseline and regular liver & renal function tests and urinalysis.

J ADMINISTRATION INFORMATION

Patient visit	This is an in-patient protocol.
Approximate drug cost (chemotherapy only)	$ 4,800 per cycle (Regimens A and B together)

Complexity Value

Regimen	2822 Per cycle (188 value normalized to 28 days)
Pharmacy	813 Per cycle
Chemo Nursing	2009 Per cycle

K KEY REFERENCE(S)

Magrath IT, Adde M, Shad A et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 14: 925-934, 1996.

Magrath IT, Janus C, Edwards BK, et al. An effective therapy for both undifferentiated (including Burkitt's) lymphomas and lymphoblastic lymphomas in children and young adults. Blood, 1984; 63: 1102-1111

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.