Kent and Medway Cancer Network

# Network Guidance Document

# Oncological treatment of Haematology CNS Disease

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## Contents

## Introduction

- This document has been written to provide guidance on the treatment of CNS disease in the Kent & Medway Cancer Network (K&MCN).

- Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols.

- See chemotherapy prescribing proformas for details on chemotherapy / anti-cancer regimens.

- All patients will be considered for entry into a clinical trial (see appendix A).

- All patients should be discussed within a multidisciplinary team meeting before commencing treatment.

- All young people aged 16-18 must be referred to the CYP Principle Treatment Centre which for KMCN is based at the Royal Marsden Hospital. Referral to a CYP Principle Treatment Centre does not necessarily mean that treatment will be undertaken at that centre; shared care management protocols may allow some treatments to be delivered locally. Young people aged 19-24 have the option of being referred to the Royal Marsden Hospital for treatment but may choose to be treated locally.

# CNS Disease

## 1.0 Risk Factors

The risk of developing CNS disease at some point in the disease course depends mainly on the histology and distribution of disease:

**Histology**

- Low grade lymphomas are associated with a very low risk of developing CNS disease and tends to be indolent. Treatment only for symptomatic disease.
- Mantle cell lymphoma: Rare but resistant to therapy when it occurs with relapse.
- Diffuse large cell lymphomas - 6.5%
- Lymphoblastic and Burkitt's lymphomas - 16.7%, up to 50% on relapse

**High risk sites for aggressive NHL**

- Orbital disease 43%
- Testis 40%
- Peripheral blood (Aggressive NHL) 33%
- Bone (extensive) 29%
- Nasal/paranasal sinuses 23%
- Bone marrow 20%

(Liang R; Chiu E; Loke SL Hematol Oncol ; 8(3):141-5 1990)

- Epidural NHL
- Breast

Main risk in multivariate analysis are >1 extra-nodal site + elevated LDH or high IPI index (Haioun et al 2000). CSF examination should thus be part of the staging for patients with disease at these sites. MRI with contrast for those with neurorolgical symptoms/signs however trivial.

**Other high risk features**

- Massive para-aortic adenopathy
- HIV positivity
- HTLV-1 associated NHL
- Post-transplant aggressive lymphoproliferative disorders
- Richter's transformation of CLL

## 1.1 Prophylaxis for high risk patients

The assessment of risk of CNS involvement is controversial and data is lacking. About 5% of patients with DLBCL develop CNS lesions.

The optimum approach to CNS prophylaxis is uncertain.

On the basis of current data CNS prophylaxis should be considered in the following circumstances:

1. Primary testicular lymphoma and breast DLBCL
2. High risk of direct invasion of the CNS (orbit, sinus, etc)
3. DLBCL with more than 1 extranodal site plus raised LDH
4. Burkitt lymphoma

*Suggested Prophylaxis*

The following treatments are used in the UK as CNS prophylaxis:

1. Within the CHOP 14 vs. 21 trial *Intrathecal* (IT) methotrexate 12.5mg is given with the first 3 courses.

   Patients with previous history of mucositis with methotrexate should routinely receive folinic acid rescue 24 hours post intrathecal methotrexate.

2. High dose IV Methotrexate 3.0 g/m$^2$ with Folinic Acid rescue for at least 3 courses sandwiched with systemic therapy. See high dose MTX guidelines.

Burkitt's or Burkit's like Lymphoma; according to protocol (eg CODOX-M/IVAC)

A.L.L.: Trial entry encouraged. High dose MTX, intrathecal chemotherapy and prophylactic cranial irradiation or TBI pre transplant Maintenance IT therapy.

For the older patient (>65 years)

a) If Creatinine clearance ≥ 50ml/min:

High dose IV Methotrexate 1.5 g/m$^2$ with Folinic Acid rescue for at least 3 courses sandwiched with systemic therapy. See high dose MTX guidelines.

b) If Creatinine clearance <50 ml/min:

Lumbar puncture at diagnosis. If positive treat with intra-thecal therapy as below. If negative, no prophylaxis is recommended.

## 1.2 Treatment of the CNS involvement by systemic lymphoma

### Meningeal lymphoma

Combination of intrathecal and systemic therapy is normally given.

### Primary Brain / Spinal Cord Lymphoma

Treat as per secondary CNS disease.

### Intrathecal chemotherapy

Consider the use of Liposomal Cytarabine* (Depocyte®) in these cases because of its long half life (141 hours) compared to 3.4 hours for standard Cytarabine and the convenience of giving it once every 14 days until CR. Maintenance can be as for triple IT below.

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| Depocyte | 50 mg intrathecal |
| Methotrexate | 15 mg intrathecal |
| Dexamethasone 4 mg bd po for 4 week then taper. | |

*NB pending funding approval or where exceptional circumstances can be evidenced through ITP route

Triple intrathecal chemotherapy is an alternative but needs more frequent treatments (twice weekly until clear CSF) and may be given via Omaya reservoir

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| Methotrexate | 12.5 mg intrathecal |
| Cytosine Arabinoside | 70 mg intracthecal |
| Hydrocortisone | 50 mg intrathecal |

Oral Dexamethasone may also need to be given if patient experiences headaches. Patients with previous history of mucositis with methotrexate should routinely receive folinic acid rescue 24 hours post intrathecal methotrexate.

Take CSF sample for chemistry, cell count, microbiology and cytology prior to chemotherapy. Treatment is twice weekly until CSF remission, then once a week x 4 and subsequently every 2 weeks until RT if indicated.

**Systemic chemotherapy**

CODOX-M / IVAC (with Rituximab for B-Cell NHL; in accordance with K&MCN list of approved rituximab indications) offers both systemic and CNS directed therapy and should be the treatment of choice particularly in the presence of systemic disease. 4-6 cycles recommended.

Otherwise, for the older or unfit patient: High dose Methotrexate (3-8 $g/m^2$) and/or high dose Cytarabine ($3g/m^2$ bd for 3 days) for a minimum of 6 cycles. ABMT should be considered for the younger patient.

Topotecan (funding approval required), Idarubicin and thalidomide (funding approval required) can cross the BBB and may be considered for second line therapy.

**Intraventricular chemotherapy**

An Omaya reservoir should rarely be needed in the acute setting, but they may be considered for palliative maintenance treatment in resistant cases. If the patient is referred with an Omaya reservoir in situ, or lumbar puncture is technically impossible and a reservoir is required.

Under aseptic technique insert an orange (G25) butterfly into the reservoir, take CSF sample for cytology, cell count, microbiology and chemistry prior to chemotherapy. Inject very slowly flushing the last injection with 1 ml filtered 0.9% sodium chloride (0.9% sodium chloride drawn through a sterile microbiological filter). Treatment is as per intrathecal chemotherapy schedule. Patients with previous history of mucositis with methotrexate should routinely receive folinic acid rescue 24 hours post intrathecal methotrexate.

**Radiotherapy**

If the patient achieves a PR/CR with intrathecal/systemic therapy or is too frail to receive this, whole brain cranial or spinal radiotherapy with a boost to the tumour bed should be given, dose and technique are outlined in the Kent Oncology Centre Disease Management and Clinical Protocols Medical Physics and Radiotherapy Quality Systems Manual: Section Central Nervous System (QDMC 26). Localised lymphomatous masses can be considered for low dose palliative radiotherapy. Radiotherapy doses should be kept as low as practical to reduce the risk of leucoencephalopathy.

There should be a gap of at least 2 weeks, preferably 4 weeks between intrathecal treatment and radiotherapy due to the risk of leucoencephalopathy. Patients should be covered by oral Dexamethasone during radiotherapy but should be weaned off the drug as soon as it is clinically practical.

## Appendix A: Clinical Trials

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

**Contact numbers**

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| **MTW – Clinical Trials Office** | 01622 225 033 |
| **Darent Valley Hospital – Clinical Trials Office** | 01322 428 100 ext 4810 |
| **Medway Maritime Hospital – Clinical Trials Office** | 01634 825 094 |

**East Kent Hospitals – Clinical Trials Office:**

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| Solid Tumours (excluding Gynae) | 01227 866 393 |
| Gynae Clinical Trials | 01843 234 343 |
| Haematology Clinical Trials | 01227864 129 |

## Document Administration

The document is located in the Kent and Medway Cancer Network office, in hardcopy and electronic format. It is also located on the Kent & Medway Cancer Network Intranet ( http://www.kentmedwaycancernetwork.nhs.uk/ ).

### DATE OF NEXT REVIEW

This item is next to be reviewed in July 2012 by the ratifying Haematology Non-Surgical Oncological Group (HOG).

## Approval Record

This document requires approval by:

| Approval Date | Name / Title | Signature |
|---|---|---|
| | Maadh Aldouri<br>Consultant Haematologist & Chair of the HOG &DOG<br>Medway Maritime Hospital<br><br>Marion Dinwoodie<br>Chair K&MCN Chief Executive Board<br>CEO Medway PCT | |

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