Haematology Cancer Clinical Guidelines

Haematology Expert Advisory Group (EAG)
on behalf of Northern Cancer Alliance

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Version History:

Date:	10.04.18	**Version:**	V17– section 11	**Review Date:**	November 2019

Document Control

Version	Date	Summary	Review Date
V17			

Date Agreed: Haematology EAG members agreed the Guidelines on:
Emailed to group on 12.04.18 for endorsement at the next meeting
Review Date: November 2019

CONTENTS

GUIDELINES FOR THE MANAGEMENT OF HIGH GRADE B CELL NON-HODGKIN LYMPHOMA (NHL)

These guidelines will cover the management of:

- Diffuse large B cell lymphoma (DLBCL), including primary cerebral lymphomas
- Burkitt lymphoma
- Primary mediastinal large B cell lymphoma

FOR ALL PATIENTS, CLINICAL TRIAL OPTIONS SHOULD BE REVIEWED PRIOR TO COMMENCEMENT OF TREATMENT

DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

1. Investigations

- Full blood count
- Renal and liver function tests, bone profile, urate, LDH
- HIV, hepatitis B and hepatitis C serology
- Bone marrow aspirate and trephine biopsy for staging, if abnormal blood count or clinical suspicion of bone marrow infiltration by low grade lymphoma
- CT scan of the neck chest, abdomen and pelvis
- Baseline FDG-PET/CT scan – when treatment is given with a curative intent
- Measured or estimated creatinine clearance if serum creatinine abnormal
- Assessment of left ventricular function by MUGA or Echocardiogram for patients with previous cardiac history or age > 60 years

2. International Prognostic Index (IPI)

The IPI should be calculated to allow risk group assignment, and will aid in the counselling of patients and their families. Either the index for all patients or the age-adjusted index (for patients < or > 60 years) may be used. The age adjusted IPI only uses three factors: LDH, stage and performance status.

Criteria: age > 60 years
LDH above normal range
> 1 extranodal site
clinical stage III or IV disease
ECOG performance status 2-4

Risk groups are assigned as follows:
Number of risk factors:

IPI risk group	All patients	Age adjusted IPI
Low	0,1	0
Low/intermediate	2	1
High/intermediate	3	2
High	4,5	3

Prognosis can be estimated according to risk group:

For all patients:

IPI risk group	CR(%)	RFS(%,5yrs)	OS(%,5yrs)
Low	87	70	73
Low/intermediate	67	50	51
High/intermediate	55	49	43
High	44	40	26

For aged 60 years or under:

IPI risk group	CR(%)	RFS(%,5yrs)	OS(%,5yrs)
Low	92	86	83
Low/intermediate	78	69	66
High/intermediate	57	53	46
High	46	58	32

For aged > 60 years:

IPI risk group	CR(%)	RFS(%,5yrs)	OS(%,5yrs)
Low	91	46	56
Low/intermediate	71	45	44
High/intermediate	56	41	37
High	36	37	21

3. Treatment of non-bulky stage IA disease

Non-bulky stage IA disease is treated by a combined modality approach, with 3 cycles of CHOP or CHOP-R followed by involved field radiotherapy. A PET scan is required to confirm stage.

4. Treatment of all other patients

There are currently no first line NCRI treatment studies open for recruitment but review updated portfolio at time of patient discussion at MDT.

Patients whose diagnostic material is deemed adequate may be approached re entry into the observational study MaPLE: Molecular profiling for lymphoma study. This study aims to aid identification of patients who may be suitable for specific targeted therapies

Patients aged between 15 and 29 are also eligible for the Non Hodkgins Lymphoma in Young Adults study: A prospective UK population-based study of incidence, treatment and outcomes of patients in the above age group with all subtypes of Non Hodgkins lymphoma diagnosed between January 2015 and December 2017

Horizons: To evaluate patient experience and health and well-being over time, questionnaire based

All new patients should be discussed at MDT for review of histology and imaging to inform the treatment plan. Staging CT and PET are required unless there are clinical reasons why PET cannot be performed as planned.

The MDT proforma should document any sites of bulk disease and bony involvement.

The current recommendation is treatment with the CHOP-R-21 regime. The usual total number of cycles intended should be 6, with a repeat CT scan after 3 cycles to confirm disease response. Earlier scanning may be required if there is a suspicion of clinical non-response or disease progression.

PET-CT scan 6 weeks post R-CHOP cycle 6 is the preferred method of assessing disease response for those patients with no features of bulk. If radiotherapy is planned, (see indications below) in most circumstances the PET scan should be performed 3 weeks post chemotherapy. If the patient has extensive disease and there is concern about achieving a complete response then the PET scan should be performed at 6 weeks post chemotherapy in order to achieve maximal sensitivity of the PET.

5. Indications for Radiotherapy

Stages IA-IIA

Usually 3 cycles of CHOP or CHOP-R plus involved field radiotherapy are recommended.

Stages IIB-IV

Radiotherapy may be given to sites of residual tumour activity (as assessed by PET-CT scan) following chemotherapy to convert PR to CR or good PR, sometimes followed by high dose chemotherapy with stem cell rescue as consolidation.

Radiotherapy may also be useful to salvage localised sites of relapse.

The role of radiotherapy to initial bulk disease following a chemotherapy-induced metabolic CR is evolving. Such patients should be discussed at MDT. In general for patients with initial bulk disease (>7.5cm) radiotherapy to the site of original bulk should be considered at the end of 6 cycles of CHOP-R with a PET CT on approximately day 21 of cycle 6 and a further PET CT 12/52 after radiotherapy is completed (this final PET-CT can be omitted if the PETCT prior to radiotherapy commencement was negative).

Radiotherapy should also be considered to areas of initial bone involvement with bone destruction – typically where <3 areas are involved.

Patients with other extranodal sites of disease at presentation should have this highlighted at the initial MDT and need for radiotherapy documented on an individual basis.

Patients unfit for R-CHOP

Patients with a history of myocardial impairment or with multiple co-morbidities can present a challenge for treatment. There is some evidence to suggest that in some patients a steroid pre-phase can improve performance status sufficiently to allow conventional chemotherapy to start.
Other options include R-GCVP, reduced dose CHOP, R-DECC or referral for clinical trial with novel combinations eg Inotuzomab Ozogamicin (**INCA** - A multicentre randomised phase II clinical trial of Inotuzumab Ozogamicin plus Rituximab and CVP (IORCVP) versus Gemcitabine plus Rituximab and CVP (GemRCVP) for the first line treatment of patients with diffuse large B cell lymphoma who are not suitable for anthracycline containing chemotherapy)

Double Hit Lymphoma

The optimal treatment for this group of patients is not yet understood. It is very reasonable to consider DA-EPOCH-R given the data available to date, albeit mainly from a single centre. RCHOP and DA-EPOCH-R should both be discussed with the patient. Intrathecal chemotherapy prophylaxis against secondary CNS disease should be offered.

Grey Zone Lymphoma

For histology intermediate between DLBCL and Hodgkin Lymphoma, consideration may be given to the use of an intensive front line management for patients fit for RGDP and autologous stem cell transplant.

6. Treatment of relapsed disease

6.1 High dose treatment

High dose chemotherapy regimens are available for the treatment of relapsed DLBCL and there are no data to confirm that some are better than others. High dose chemotherapy is consolidated with an autologous stem cell transplant (ASCT) if a CR or good PR is achieved. The addition of rituximab is approved for relapse >12 months from initial R-CHOP chemotherapy.

Commonly used high dose regimes include:

GDP – Gemcitabine (days 1 and 8), Cisplatin (day 1) and dexamethasone (days 1-4) (±rituximab)

IVE – Ifosfamide (days 1-3), etoposide (days 1-3) and epirubicin (day 1) (±rituximab)
DHAP – dexamethasone (days 1-4), high dose cytarabine (day 2), cisplatin (day 1) (± rituximab)
ESHAP – etoposide (days 1-4), methylprednisolone (days 1-5), high dose cytarabine (day 1), cisplastin (days 1-4) (± rituximab)
FluDAP – Fludarabine (days 2,3), dexamethasone (days 1,3), high dose cytarabine (days 2,3), cisplatin (days 2,3)

The choice of regime must be discussed and agreed at the lymphoma MDT meeting.

6.2 Autologous stem cell transplantation (ASCT)

ASCT has become part of routine intensive treatment for relapsed DLBCL. Because under half of patients treated with ASCT will be cured, prognostic factors are important to predict outcome. An age-adjusted IPI at the time of initiation of second-line treatment is available as a predictor of event-free survival (EFS) and OS in such patients.

For patients aged 60 or under:

Risk factors:	LDH above upper limit of normal
	Stage III/IV disease
	ECOG performance status 2-4 or Karnofsky score =< 70
Low risk:	0 factor
Intermediate risk:	1 factor
High risk:	2 or 3 factors

Below is a table from the published Coral Paper showing outcomes after salvage and ABMT (Gisselbrecht JCO September 2010)

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR			3-Year Event-Free Survival		3-Year Overall Survival	
		No. of Patients	%	*P*	%	*P*	%	*P*
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saaIPI, secondary age-adjusted International Prognostic Index.

Patients with second relapse

Patient should be referred for consideration of CAR-T therapy (ALEXANDER study) or Javelin study (PD1)

Patients not fit enough for intensive treatment at first relapse

Patients should be considered for ARGO with randomised patients to the addition of atezolizumab to R-GEMOX

For other patients, various out patient-based oral palliative regimes are available. Caution should be exercised as such combination regimes may be significantly myelotoxic, especially in the elderly, and lead to the risk of neutropenic sepsis.

CEPP – cyclophosphamide (day 1), etoposide (days 1-3), procarbazine (days 1-10), prednisolone (days 1-10)
DECC – lomustine (day 1), etoposide (days 1-3), chlorambucil (days 1-4), dexamethasone (days 1-5) (This is the new version of PECC – see page 92.)
PIXANTRONE : NICE approval granted for use in patient who have previously received rituximab and who are requiring either 3rd or 4th line therapy.

7: Central nervous system (CNS) prophylaxis

The highest risk patients are identified by anatomical site of diease involvement and also CNS IPI score.

CNS prophylaxis should be offered to patients with **renal, adrenal, breast , testicular disease and double hit lymphomas. (NICE guidance)**

Offer prophylaxis to patients with **4 points or more on CNS IPI** as below (CNS IPI: Schmitz et al JCO 2016;34(26):3150-3156

CNS IPI Risk factors : 1 point scored for each risk factor

(2 yr risk CNS disease 0.6% in low risk group, 3.4% in int med gp, 10.2 % in high risk)

LDH
Age above 60
Performance status >1
>1 Extranodal site
Stage III or IV
Renal or adrenal

Optimal approach to how to deliver chemotherapy prophylaxis is uncertain. It is essential that proven curative RCHOP therapy is not delayed by the delivery of unproven prophylaxis. Currently intrathecal methotrexate 12.5mg with each cycle of CHOP-R for 4 cycles is used for the majority of patients requiring prophylaxis.

The use of high-dose intravenous methotrexate can be considered in some patients and the effect on any treatment delays and in-patient resource requires auditing for these patients. Currently the decision is left to the discretion of individual clinicians and MDTs.

7. Treatment of Primary CNS lymphoma

Key recommendations in the investigation and management include:

Full CT scan staging, MRI head and MRI spine, testicular ultrasonography in males, lumbar puncture for CSF analysis (including cytology, protein, glucose, flow cytometry and Ig gene rearrangement studies), slit lamp examination of the anterior chamber, vitreous and fundus of the eye, and HIV serology

Stereotactic biopsy should be carried out prior to the use of corticosteroids if at all possible

Prognostic score should be calculated according to age (>60 years), ECOG performance status (>1), raised LDH, raised CSF protein, and involvement of deep brain matter (Ferreri et al, 2003).

Risk group	Factors	2-year OS
High	4-5	15%
Medium	2-3	48%
Low	0-1	80%

Dexamethasone may be used as short-term palliation.

All patients sufficiently fit should be offered chemotherapy.
Following presentation of preliminary results of the IELSG study at Lugano 2015 the recommended regime is **MATRIX**

Rituximab 375 mg/m^2 Day -5 and Day 0
Methotrexate 3,5gm/m^2 Day 1
Ara C 2 gm/m^2 x 2 Days 2 and 3
Thiptepa 30 gm/m^2 Day 4

Treatment is given every 3 weeks with repeat MRI after course 2 to ascertain response.
The aim is to deliver 4 cycles.

Consolidation with ABMT for patients achieving CR PR and SD

Consolidative whole brain radiotherapy (WBRT) for non-responders should be discussed with patients on an individual basis as the risks of neurocognitive deficit may out-weigh benefits especially in those over 60 years.
Intrathecal chemotherapy as an adjunct to high-dose MTX is not indicated.
Treatment of relapsed or refractory disease will depend on patient's performance status.

Options include:

TIER clinical trial: A phase 1/11 Study of Thiotepa, Ifosfamide, Etoposide and Rituximab for the treatment of relapsed and refractory primary cerebral lymphoma.
Salvage chemotherapy
Whole brain radiotherapy
Palliative steroids

Treatment of Secondary CNS Lymphoma

No consensus treatment guidelines are available.

Treatment options will depend on nature of CNS involvement eg meningeal or space occupying lesion and on treatment intent. In most patients this is likely to be a palliative situation and symptom control is paramount.
Options could include intra-thecal chemotherapy for meningeal disease, chemotherapy or radiotherapy. Suggest MDT discussion to guide treatment decisions.

IELSG 42: An international Phase 11 trial assessing tolerability and efficacy of sequential Methorexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen) closed to recruitment in July 2018. Results are awaited but it is reasonable to follow his protocol if the patient is fit.

BURKITT LYMPHOMA

This malignancy is defined as a germinal centre cell lymphoma with deregulation of the c-myc oncogene, and absence of other balanced translocations. There is an association with HIV infection and, as with all lymphomas; this should be tested for prior to chemotherapy.

It is characterised by:

morphologically, large B cells with round nuclei, central nucleoli and vacuolated cytoplasm

immunohistochemically, SmIg+, CD10+, bcl-6+, bcl-2-, high proliferation index Ki67 (≈100%) and evidence of apoptosis, and cytogenetically, t(8;14) or variants by FISH.

Primary treatment:

Patients should be treated at a BCSH level 2b centre or above.

-CODOX-M/R-IVAC regimen is recommended. Patients should be entered into clinical trial where possible.

Rasburicase should be used before and during the first cycle of treatment. Frequent biochemical measurements paying special attention to renal function, potassium, calcium and phosphate levels should be carried out. Twice daily measurements may be required over the first few days. Urate level is rarely helpful in patients who have received rasburicase as it will almost always be unrecordable.

There is increasing evidence that DA-EPOCH-R can be used to treat Burkitt Lymphoma effectively. Whilst we have not moved wholesale to this approach, DA-EPOCH-R is easier to tolerate than R-CODOX-M or R-IVAC and thus could be considered in some patients thought unfit for the latter regimens. The HOVON RCT comparing both regimens is due to open 2018/2019.

Relapsed disease:

There is no consensus or trial. The outcome is very poor.

PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA (PMLBCL)

PMLBCL is a distinct clinico-pathological entity recognised by the WHO. Pathologically it is derived from B cells, but has clinico-pathological features and molecular characteristics reminiscent of nodular sclerosis classical Hodgkin lymphoma.

Primary treatment:

Using historical comparisons, dose-dense and dose-intense regimens may be more effective than CHOP chemotherapy (before the advent of rituximab), but there are no phase III trial data to support this.
Currently DA EPOCH-R, CHOP-R or R-MACOP-B as primary treatments for PMLBCL are all used.

It is recommended where possible that patients are entered into the IELSG 37 clinical trial: A randomised, open-label, multicentre, two-arm Phase 111 comparative study assessing the role of mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL). This study is using a PET directed approach to answer the question of whether radiotherapy is required in those patients who become PET negative after primary chemotherapy.

Outside a clinical trial our current chemotherapy preference is for DA EPOCH-R but it is reasonable for clinicians to discuss choice of regimen on a case by case basis with patients.

Consolidation radiotherapy should be considered for patients. PET scan may inform decision making for consolidation radiotherapy: see IELSG 37 information above. All patients should discuss the risks and benefits of consolidation radiotherapy with a clinical oncologist.

Relapse treatment:

Treatment failures tend to occur within the first 6-12 months. Relapses beyond 2 years are rare. Relapse treatments should be as for DLBCL.

References:

7 NICE website: www.nice.org.uk

8 Yorkshire Cancer Network guidelines website: www.ycn.nhs.uk/html/downloads/ycn-haematology-guidelines2008.pdf

9 BCSG guidelines website: www.bcshguidelines.com/pdf/PCNSL_guidelines.pdf