Lancashire and South Cumbria Haematology NSSG Guidelines for Burkitt's and Burkitt's-like lymphoma

1.1 Pre-treatment evaluation

The following tests are to be performed at presentation followed by MDT discussion:

- FBC, U&Es, creat, LFTs, calcium, phosphate, LDH, immunoglobulins
- PET-CT scan where treatment is with curative intent, or at least a CT scan of neck, thorax and abdomen if PET-CT scan is not possible
- MRI scan where possible for assessment of disease in the naso- and oropharynx and Waldeyer's ring, sinuses, CNS and paraspinal areas where there is a suspicion of spinal cord compromise.
- Bone marrow aspiration and trephine biopsy unless knowledge of marrow infiltration will not affect management e.g an elderly patient with stage III disease, palliative management, circulating lymphoma blasts present on blood film
- Assessment for CNS disease: CT +/- MRI scan of brain, CSF cytospin cytology (note that it is critical to establish whether there is CNS disease hence intrathecal chemotherapy must only be given when it is certain an adequate baseline CSF cytospin sample has been obtained)
- Hepatitis B, C and HIV serology
- Assessment of cardiac function in patients with a history of or risk factors for cardiac disease
- Determination of stage, bulk disease and risk group (appendices 1, 2).

It must be noted that Burkitt's lymphoma is often a particularly aggressive form and patients are at high risk of tumour lysis syndrome and organ failure, hence prompt evaluation and commencement of therapy is vital. Patients for other than palliative management must be referred to Blackpool Teaching Hospitals at the earliest opportunity.

Where the diagnosis is unclear e.g initial histology indicates an aggressive B-cell lymphoma and further studies such as FISH are awaited, and there is an urgent need to start treatment, give one cycle of R-CHOP.

1.2 Post-treatment evaluation

- On completion of treatment the patient must be reassessed clinically and where treatment is given with curative intent all abnormal tests at baseline repeated followed by MDT discussion with review of an end of treatment PET-CT scan performed at least 6 weeks after the last dose of chemotherapy.

2. Patients fit enough for R-CODOX-M/R-IVAC and R-EPOCH chemotherapy

2.1 Principles

- Although many patients may be cured if treated with very intensive chemotherapy regimens such as RCODOX-M/R-IVAC**,** this associated with significant treatment-related morbidity and mortality especially in patients over 50 years of age. Dose-adjusted R-EPOCH is a less intensive and better tolerated regimen which has also been used with success to treat patients 60-80 years old. It remains unclear whether

R-EPOCH is as effective as R-CODOX-M-R-IVAC but it is probably less effective in patients with high risk Burkitt's lymphoma.

- It must also be noted that unlike R-CODOX-M/R-IVAC, R-EPOCH does not incorporate systemic CNS-penetrating agents, relying instead on intensive intrathecal chemotherapy for CNS-prophylaxis and treatment. R-EPOCH is less effective in patients with CNS disease at presentation and is associated with a high rate of CNS relapse in patients at higher risk of CNS disease.
- Choice of treatment must therefore be made after a careful evaluation of risk group, the presence of CNS disease and whether parenchyma/leptomeningeal, risk of future CNS relapse, organ, function and comorbidity. Note that R-EPOCH in patients with CNS disease requires intensive intrathecal chemotherapy (see 2.2.)
- It is possible to identify a small group of patients with Burkitt's lymphoma (approx. 10%) who have 'low risk' disease and who have a very good prognosis when treated with R-EPOCH and without intrathecal chemotherapy. 'Low risk' in this guideline is defined (after Roschewski et al.[1]) as the presence of **all** of:

  stage I/II disease, normal LDH, ECOG score ≤ 1, no tumour mass >7cm
- The Burkitt's lymphoma IPI[2] (appendix 2) may also be useful in guiding management.
- Note that interim PET scans are used to guide the duration of therapy where patients are being treated with R-EPOCH (Roschewski et al, 2020). However, a formal scoring system for PET positivity e.g Deauville score, was not used in these studies. Scans were score as 'positive' or 'negative'.

2.2 Low risk disease

- In patients < 50 years without comorbidity, fit enough for R-CODOX-M-R-IVAC:

  R-CODOX-M x 3 (includes IT chemotherapy as per protocol)

  or

  R-EPOCH x 2, then interim PET scan. If PET -ve further R-EPOCH x 1, no IT prophylaxis. If PET +ve R-EPOCH x 4 plus intensive IT prophylaxis.
- In patients > 50 years or < 50 years and unfit for R-CODOX-M/R-IVAC:

  R-EPOCH x 2, then interim PET scan. If PET -ve further R-EPOCH x 1, no IT prophylaxis. If PET +ve R-EPOCH x 4 plus intensive IT prophylaxis.

Note: intensive IT <u>prophylaxis</u> with R-EPOCH:

Day 1 and 6 in cycles 1-4 (8 doses), alternating methotrexate/cytarabine

2.3 High risk disease

- In patients < 50 years without comorbidity, fit enough for R-CODOX-M/R-IVAC:

  R-CODOX-M/R-IVAC x 2 (includes IT chemotherapy as per protocol)
- In patients > 50 years or < 50 years with comorbidity or less fit:

  R-EPOCH x 6 plus intensive IT chemotherapy

  or

R-CODOX-M/R-IVAC x 2 remains an option after careful consideration of the risks and benefits and especially if there is CNS disease at presentation or the patient is at high risk of later CNS relapse e.g stage IV, marrow infiltration.

- Intensive IT prophylaxis for high risk patients without CNS disease on R-EPOCH:

  Days 1 and 6 for cycles 1-4 (8 doses) with alternating methotrexate/ cytarabine

- Intensive IT chemotherapy treatment for patients with CNS disease on R-EPOCH:

  IT chemotherapy twice/week with alternating methotrexate/cytarabine for weeks 1-4, then once weekly for 6 weeks, then monthly for 6 months.

3. Patients not fit for intensive therapy

- Options are R-CHOP, mini-R-CHOP, palliation

4. Relapsed/refractory disease

- The prognosis for relapsed/refractory Burkitt's lymphoma is poor with only occasional patients achieving a durable response after second line therapy +/- transplantation. Hence palliative management must be considered.
- Optimal second line therapy is not known – options are DHAP+/-R, MATRIX regimen, R-IE depending on age, performance status, presence of CNS disease, duration of remission, organ function.
- If remission can be achieved referral for consideration of allogeneic transplantation or autologous transplantation must be considered.

References

1. Roschewski et al. Multicenter study of dose-adjusted EPOCH-R in adults with untreated Burkitt's lymphoma. J Clin Oncol (2020), 38(22), 2519-29
2. Olszewski et al. Burkitt's lymphoma International Prognostic Index. J Clin Oncol (2021), 39(10), 1129-38

Appendix 1: Definition of low risk disease (after Roschewski et al [1])

All of**:** normal LDH, stage I-II, < 2 extra-nodal sites, ECOG 0-1
All others considered high risk.

Appendix 2: Burkitt's lymphoma IPI (BL-IPI)

Risk factors: age >40yrs, ECOG score ≥2, LDH > 3 x upper limit of normal, presence of CNS disease

	% cases	PFS 3y	OS 3y
Low risk – 0 factors	18%	92%	96%
Intermediate – 1 factor	36%	72%	76%
High risk - > 1 factor	46%	53%	59%

Author	Dr MP Macheta
Date	20th Dec 2022

Ratified by LSCCN Haematology NSSG	
Review date:	Dec 2024