Guidance for the management of patients with lymphoma during the COVID19 health emergency: a statement from a panel of UK lymphoma experts

The COVID 19 pandemic is significantly compromising our ability to deliver safe and effective treatment for patients with lymphoma, either through direct complications from COVID-19 or from the wider impact on provision of normal clinical service. In an attempt to mitigate against risk for individual patients, together with reducing impact on core NHS service capacity, a UK lymphoma expert panel has developed interim treatment guidelines for the clinical management of adult patients during this emergency.

We recognise that there are very few data to guide decision-making in this situation. This guidance is intended to assist with, rather than replace, decision-making for individual patients and should be used alongside existing recommendations from the

o DoH (https://www.gov.uk/government/collections/wuhan-novel-coronavirus),

o NHS England (https://www.england.nhs.uk/coronavirus/)

o NICE (https://www.nice.org.uk/guidance/ng161)

- SBMT&CT recommendations for COVID v3 (see here)

o together with individual policies from NHS Trusts.

Given the rapidly changing situation, this guidance remains under constant review. Importantly, there can be no 'one size fits all' approach and deviation from standard protocols should be carefully discussed with individual patients, with a clear risk: benefit analysis documented in the case notes and agreed at MDT wherever possible.

1. General principles

Try to minimise or avoid visits to the hospital for treatment, scans or follow-up appointments.

Wherever safe to do so:

• Conduct consultations by telephone or videoconference to reduce hospital footfall –

including patients on treatment

• Lengthen the interval between hospital appointments

• Avoid interim imaging in patients clinically responding to therapy, unless interim imaging

is used to direct therapy within a standard protocol (e.g. interim PET in first line HL)

• Avoid bone marrow aspirates and trephine for staging

• Consider abbreviating treatment where no overall survival advantage is expected

• Consider reducing the intensity of treatment to lower the risk of myelosuppression and

immunosuppression, but balance this carefully against the risk of treatment failure

• In line with NHSE interim guidance, give prophylactic daily granulocyte-colony stimulating factor (G-CSF) or a biosimilar PEGylated G-CSF to prevent neutropenic fever and reduce admissions (for example, for patients on chemotherapy regimens with a greater than 10% risk of neutropenic fever)

- For clinical trials that remain open, please refer to trial-by-trial guidance from the study

sponsor and your institution.

2. NICE approved interim treatment change options during the COVID-19 pandemic

NHS England endorsed interim treatment options effective from 23rd April 2020 for cancer patients during the COVID-19 pandemic. These offer less immunosuppressive or resource intensive options without compromising NHS capacity or service delivery. A full list of changes can be found at https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381

3. COVID-19 trials

Numerous COVID-19 trials are running in the UK. Consider enrolling eligible COVID-19 positive patients into a relevant study, wherever possible.

- A current list of open trials can be found at https://www.nihr.ac.uk/covid-studies/.
- Details of the Coronavirus Cancer Monitoring study can be found at https://ukcoronaviruscancermonitoring.com/

4. Treatment guidance for patients with Hodgkin lymphoma

As Hodgkin lymphoma is curable in most patients, delivery of dose- and time-intensive treatment remains a high priority.

a. Early stage HL

• Combined modality approach with reduced number of chemo regimens should be considered. Options would include:

o ABVD x 2 + 20Gy ISRT for early favourable

o 'Rapid' approach: ABVD x 3 and then no further treatment if PET neg or a 4th and RT if PET positive (omitting RT would reduce footfall to the hospital considerably)

o ABVDx4 and ISRT for early unfavourable

b. Advanced stage HL

• A RATHL approach for most patients appears optimal. Escalated BEACOPP / BEACOPDac is more intensive and very steroid rich although for very poor risk patients it may still be optimal. Reducing the prednisolone to 7 days should be considered (this is standard in some countries)

• Consider no radiotherapy to initial bulk if interim PET (iPET2) negative (standard of care in many centres now)

• Interim PET (iPET2) scanning is still advisable in order to have confidence to omit the bleomycin after 2 cycles. If iPET2 is positive, escalated BEACOPP / BEACOPDac is not proven in a randomised trial to be of benefit. If iPET2 is Deauville score 4 then consider completing 6 cycles of ABVD and at the end of treatment using consolidation radiotherapy to sites of iPET2 DS 4 positivity. Patients with a Deauville 5 score at iPET2 should still be considered for a change in treatment: escBEACOPDac, BEACOPP-14 or a salvage approach.

• For patients who are interim PET negative (iPET2), consider omitting end of treatment scan.

c. Elderly Hodgkin in ABVD / AVD unfit

• Radiotherapy alone can be considered for early stage

• A period of watch and wait maybe considered for asymptomatic patients

• If systemic treatment is needed, suggest dose modifying regimens (e.g. ChlVPP, VEPMB) and using reduced number of cycles to enter a remission

d. Relapsed Hodgkin

• If early stage / low volume, could defer treatment although needs careful discussion with patient

• Consider outpatient chemotherapy regimen for 1st line relapse such as GDP

• Bendamustine is particularly T-cell suppressive and should probably be avoided

• For early stage relapse, consider radiotherapy as consolidation without a stem cell transplant (although would need to be explained this is not standard of care)

• Single agent brentuximab and PD1 inhibitors are quickly administered and so are probably safer than multi-agent chemotherapy, so should be used where possible in the treatment pathway.

- Autologous stem cell transplantation should still be considered if the patient is suitable and agreed by the transplant centre.

• Allogeneic stem cell transplant is the most immunosuppressive procedure that can be performed and should if possible be avoided during the COVID-19 pandemic.

e. Nodular LP Hodgkin

• Watch and wait if possible, radiotherapy for symptomatic site or single agent rituximab

• If chemotherapy is needed, suggest R-CVP unless high grade transformation in which case R-CHOP is indicated.

• Consider Rituximab monotherapy if available

5. Suggested treatment for patients with low grade Non-Hodgkin lymphoma

a. Previously untreated FL, MZL and LPL patients

• Consider watchful waiting for patients not requiring immediate therapy

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• If symptom control is required, consider local radiotherapy, corticosteroids or single

agent rituximab

• For those requiring systemic therapy, consider less myelosuppressive regimens e.g.

R-CVP or O-CVP (for FL). If on bendamustine or CHOP, consider dose reductions e.g.

day 1 bendamustine only. Use GCSF (or pegylated GCSF in line with NHSE interim change options) routinely if using R-CHOP and bendamustine asper local policy.

• Try to avoid escalating therapy unless patients have progressed or the risk of COVID19 infections/infectious complications has significantly reduced.

- For follicular lymphoma patients receiving rituximab with lenalidomide, a switch from intravenous rituximab to subcutaneous rituximab from dose 5 has been approved by NHSE as an interim option

• Consider deferring planned transplant consolidation, where possible. Liaise with transplant team where appropriate and follow the BSBMT&CT guidance.

b. Previously untreated MCL patients

• Consider watchful waiting for patients not requiring immediate therapy

• If symptom control is required, consider local radiotherapy or corticosteroids

- Oral ibrutinib (with or without rituximab) has been approved by NHSE as an interim first-line treatment option instead of intravenous chemotherapy

• For transplant-fit younger patients (65 and less), high dose cytarabine regimens remains optimal, however R-ibrutinib or R-B may provide affective but less intensive alternative induction regimens

If using a Nordic approach, standard dose CHOP is acceptable. An autograft in this

situation would be relatively low priority.

• For older, fit patients, consider oral ibrutinib +/- R or R-CHOP with GCSF cover and consider maintenancerituximab when possible. Bendamustine should probably be avoided.

• Consider oral ibrutinib +/- R, dose reduced R-CHOP, R-CVP or R-chlorambucil for older/frailer patients.

c. Any patients on induction treatment

• Consider switching to a less myelosuppressive regimen especially if patients are experiencing infective complications, myelosuppression or hypogammaglobulinaemia.

• Consider shortening the course of treatment e.g. 4 cycles instead of 6 for patients responding to treatment.

• Try to avoid escalating therapy unless patients have PD or have transformed.

d. Patients on maintenance treatment

• Consider temporarily stopping (or not starting) maintenance therapy for all patients. Maintenance therapy may be started/re-started after the pandemic, especially for patients with mantle cell lymphoma

• Consider deferring planned transplant consolidation, where possible. Exceptions include patients with blastoid histology and/or a rapidly progressive pre-treatment disease course. Liaise with transplant team where appropriate and follow the BSBMT&CT guidance.

6. Treatment guidance for patients with aggressive non-Hodgkin lymphoma

For most patients with aggressive lymphoma subtypes, treatment is delivered with curative intent so this remains the clinical priority.

a. First-line treatment Burkitt lymphoma

• First-line therapy with standard protocols (R-CODox-M/R-IVAC or DA-EPOCH-R) remain the recommended approaches for BL. Use of ambulatory care to reduce exposure time to hospital should be accommodated wherever possible. For CODoxM, consider giving the methotrexate 3g/m2 over 3h as probably less toxicity.

b. First line treatment for DLBCL (includes DHL and histological transformation of indolent NHL)

• Consider R-CHOP with GCSF support cover for the vast majority of patients with all (non-Burkitt) aggressive B cell lymphomas. There are no randomised data to support a survival advantage of using more intensive regimens, which are likely to confer additional risk during the COVID-19 pandemic

• Consider the omission of consolidation radiotherapy to bulk unless there is convincing evidence of residual disease on the end-of-treatment PET-CT

• Where radiotherapy is employed, consider a hypofractionated approach

• Consider restricting CNS prophylaxis to those in the highest risk groups (e.g. testicular, adrenal or renal involvement)

c. First-line treatment of primary mediastinal B cell lymphoma (PMBL)

• Consider using RCHOP14 as a dose-intensive outpatient regimen

• Randomised evidence to support the omission of consolidation radiotherapy after RCHOP is not yet available although retrospective data supports this. Consider omission for those who are PET negative at EOT.

• Consider hypofractionated radiotherapy consolidation in line with current guidance

• If DA-EPOCH-R can be delivered in an ambulatory setting and the strategy is to omit consolidation radiotherapy for those in CR, this may be a reasonable option for selected patients

d. First line treatment of primary CNS lymphoma

• Please refer to existing BSH guidance for primary CNS lymphoma

• Consider reducing the number of dose cytarabine doses per cycle within the MATRix regimen to avoid early toxicity, prolongation of inpatient stay and reduced risk of admission to intensive care. Also consider reducing / omitting thiotepa in patients > 60 or 65 years, taking into account PS and co-morbidities.

• However, such decisions need to be balanced carefully against the risk of early disease progression and the consequences thereof.

• For ASCT consolidation, consider reducing the thiotepa dose to a total of 10mg/kg (rather than 20mg/kg) given that there are no data to support superiority of 20mg/kg over 10mg/kg and that the higher dose is associated with higher toxicity, risking a longer inpatient stay and risk of ICU admission.

e. Treatment of secondary CNS lymphoma

• Treatment pathways and protocols are expected to largely follow existing practice

with additional consideration for dose reductions of myelosuppressive chemotherapy agents, carefully balancing risk and benefit for individual patients

f. Peripheral T cell lymphomas

• CHOP with GCSF support remains the standard of care for first-line therapy of peripheral T cell lymphomas

• On an individual patient basis, consider the omission of ASCT consolidation, for which a survival benefit has not yet been clearly established.

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g. Relapsed/refractory aggressive lymphoma

• Treatment pathways for relapsed aggressive lymphoma are largely expected to follow existing pathways with the caveat that restricted bed and/or ICU capacity at some institutions *may* restrict therapies such as stem cell transplantation and/or CAR-T cell therapy.

- Interim NHSE guidance has allowed the use of polatuzumab vedotin (in combination with bendamustine and rituximab) for DLBCL as bridging therapy for patients approved for CAR-T therapy, both before and after apheresis

• Wherever possible, deliver salvage regimens in the ambulatory setting

• Consider restricting multi-agent salvage therapy to those patients on a curative pathway

Writing group

This guidance represent the opinions of a subgroup of the NCRI Lymphoma Research Group (Chair Andrew Pettitt) and have been coordinated by the subgroup chairs Graham Collins, Kim Linton, Chris Fox with the help and suggestions by Kirit Ardeshna, Mark Bishton, Cathy Burton, David Cutter, Kate Cwynarski, George Follows, Timothy Illidge, Sunil Iyengar, Peter Johnson, Rod Johnson, Pamela McKay, Andrew McMillan, Tobias Menne, Wendy Osborne, Beth Phillips, John Radford and Simon Rule.