
Pan-London Haemato-Oncology Clinical Guidelines

Lymphoid Malignancies
Part 1: Hodgkin Lymphoma

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

Hodgkin lymphoma (HL) accounts for approximately 15% of lymphomas in the UK; around 1,700 people are diagnosed with HL each year with a slight male predominance (<https://www.hmrn.org/statistics>). The majority of these cases fall under the category of 'classical HL' (cHL) while the remaining are nodular lymphocyte predominant HL (NLPHL). The latter is a separate disease entity from cHL and more information on NLPHL can be found in section 12.

Classical HL is the most common form of haematological cancer in teenagers and young adults and has a peak incidence between 15 and 35 years. After young adults, the most frequently affected age group are adults aged over 55, although any age group can be affected. It is extremely rare in young children.

Overall, patients with cHL have a good outcome and the majority are cured with first-line treatment. With current treatment, approximately 80% of patients survive this lymphoma.

When considering treatment options for Hodgkin lymphoma, the medium and long-term toxicities need to be considered and therefore treatment is highly individualised by factors such as gender, disease distribution, age, B symptoms and bulk. It is increasingly recognised that late effects of treatment need to be considered when planning treatment. Important late effects include secondary malignancies, cardiac toxicity, subfertility, and endocrine abnormalities.

Recent international trials have focused on the de-intensification of treatment based on pre-treatment risk stratification as well as response adapted therapy using FDG-PET imaging, while limiting intensification strategies only to selected high risk cases. There is currently no international consensus as to the definition of unfavourable disease in early stage patients and recent trials have used different risk stratifications.

Despite the availability of highly effective treatment, these guidelines are written at a time where there is considerable debate and uncertainty about the optimal management of cHL, and without the benefit of long term follow-up data on late onset toxicity from recently published trials that may help clarify some of this uncertainty.

A common theme in cHL is that there is a small population (approximately 10% of patients) who do not respond well to conventional treatment. At present, there is no way of reliably identifying those patients at highest risk of treatment failure. There are a number of emerging therapeutic strategies that stand to change the way patients with refractory disease are managed in the near future.

2 Referral Pathways from Primary Care

Rapid referral for investigation of significant lymphadenopathy, especially in the presence of B-symptoms, should be made on the same day on a 2 week wait pathway.

Triggers for referral may come from an enlarged lymph node from GPs or from specialist medical or surgical teams. Most patients will present with painless lymphadenopathy and diagnosis is made from lymph node biopsy.

3 Investigation and Diagnosis

An accurate diagnosis of HL requires as a minimum a core biopsy, an adequately sized surgical specimen, or excisional lymph node biopsy. Fine needle aspiration is inadequate to diagnose lymphoma and should not be performed when lymphoma is suspected.

Whilst core biopsies are often adequate it should be noted that, due to the possibility of sampling error, where there is a high clinical suspicion of lymphoma but the core biopsy shows no evidence of lymphoma, a repeat core or excision biopsy should be performed.

The diagnosis should be made by a specialist haemato-pathologist according to the World Health Organization (WHO) classification.

There are 4 sub-types of cHL: nodular sclerosing (NS), mixed cellularity (MC), lymphocyte-rich (LR) and lymphocyte-depleted (LD) sub-types. Although these sub-types differ in terms of association with EBV, epidemiology, and clinical presentation, there is no difference in prognosis or treatment.

3.1 Initial assessment and investigation

Baseline investigations and assessments should include:

- Full blood count (FBC) + differential, erythrocyte sedimentation rate (ESR). ESR is required in early stage disease for risk stratification ([section 3.2](#)) and can guide treatment.
- Serum biochemistry: renal profile, liver profile, bone profile, uric acid, albumin, lactate dehydrogenase (LDH) and C-reactive protein (CRP).
- Serum immunoglobulins and serum protein electrophoresis.
- HIV, hepatitis B and C serology.
- Bone marrow aspirate and trephine is not required unless FDG-PET has not been performed and a positive bone marrow would lead to upstaging and/or change in management. (Cheson, Fisher *et al*, 2014)
- Baseline FDG-PET is required and should be performed with a contrast enhanced CT of the neck/chest/abdomen/pelvis.
- MUGA/ECHO for left ventricular ejection fraction measurement in selected patients, for example those with cardiac co-morbidities.
- Pulmonary function tests (optional) in selected patients with pre-existing pulmonary disease or unexplained breathlessness – request TLCO and KCO.
- Referral for fertility preservation should be made where appropriate. Options include sperm cryopreservation, egg harvesting and embryo cryopreservation. Some fertility experts recommend treatment with gonadotrophin releasing hormone agonists during chemotherapy, but there is limited evidence that this is effective. The decision to pursue fertility preservation procedures needs to be balanced carefully against the risks of delaying initiation of treatment.

3.2 Staging and risk assessment

Using the Modified Ann Arbor staging system, HL is divided into early stage or advanced stage disease (Cheson, Pfistner *et al*, 2007).

Table 1: Ann Arbor staging system

Stage	Prognostic groups
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols
A – No symptoms B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months X: Bulky disease: >1/3 mediastinum at the widest point; >10cm maximum diameter of nodal mass E: Involvement of single, contiguous or proximal, extra nodal site	

Classification of early stage cHL into favourable and unfavourable categories can guide treatment decisions. There are a number of different risk stratification systems that have been used in the trials guiding treatment of early stage disease. For example, in the UK, patients with stage II disease with B-symptoms or bulk have traditionally been treated as advanced stage cHL when planning management.

Where possible, the stratification that was used in the trial that informs the treatment being considered should be used.

The majority of clinical trial data in early stage HL has emerged from the German Hodgkin Study Group (GHSG) and The European Organisation for the Research and Treatment of Cancer (EORTC). Criteria for unfavourable disease are listed in the table below.

Table 2: Criteria for unfavourable early stage disease

Presence of any of the criteria listed places the individual in the early stage unfavourable group.

GHSB	EORTC
Mediastinal mass >1/3 maximum diameter	Mediastinal mass ≥ 0.35 maximum diameter
ESR ≥ 50 with no B-symptoms	ESR ≥ 50 with no B-symptoms
ESR ≥ 30 with B-symptoms	ESR ≥ 30 with B-symptoms
Extranodal disease	Age >50
≥ 3 lymph node sites	≥ 4 lymph node sites

In advanced stage cHL, the International Prognostic Score in Hodgkin's Lymphoma should be calculated (Hasenclever and Diehl, 1998). One point is assigned to each of the following seven prognostic factors:

- age >45 years
- male sex
- serum albumin concentration <40g/L
- haemoglobin concentration <105g/L
- Stage IV disease
- leucocytosis $\geq 15 \times 10^9/L$
- lymphopenia <0.6 $\times 10^9/L$ or <8% of total white cell count.

The rates of freedom from progression and overall survival according to the IHDPS or 'Hasenclever score' are listed in Table 3 below.

Table 3: Freedom from progression and overall survival based on IHDPS

Prognostic score	Freedom from progression	Overall survival
0	84%	89%
1	77%	90%
2	67%	81%
3	60%	78%
4	51%	61%
>5	42%	56%

3.3 The use of ^{18}F -FDG PET in cHL

HL is a highly FDG-avid lymphoma and nearly 100% of cases demonstrate high FDG uptake (Barrington, Mikhaeel *et al*, 2014).

The use of FDG-PET is recommended in the staging of HL because of greater accuracy compared with CT alone. In prospective studies, FDG-PET has been shown to upstage 13–24% of patients when compared with CT. This has the potential to significantly change the treatment required. (Follows, Ardesbna *et al*, 2014).

FDG-PET is now considered standard practice and should be performed wherever possible prior to starting treatment.

Interim FDG-PET scans are now standard of care with evidence from randomised clinical trials that early interim FDG-PET can be used to guide further therapy in both early and advanced stage disease. Interim FDG-PET in the front-line setting is recommended after the first 2 cycles of treatment except when the RAPID approach is used in early stage HL where it is performed after 3 cycles. When 2 cycles of ABVD plus 20Gy IFRT are planned, PET scan is not mandatory until after completion of radiotherapy.

It is important to note that 15% of patients with a negative interim PET treated in the RATHL trial subsequently progressed within 3 years and the negative predictive value of interim PET is therefore lower than was previously thought (Johnson, Federico *et al*, 2016).

A five-point scale, known as the Deauville scale, has been widely used for reporting response in the prospective trials that inform the new standards of care. It is recommended that response is reported according to the Deauville scale (Barrington, Mikhaeel *et al*, 2014).

PET scans should be reported by a nuclear medicine consultant experienced in the reporting of scans in patients with lymphoma.

Table 4: The Deauville scale

Deauville score	Criteria
1	No uptake
2	Uptake less than or equal to the mediastinum
3	Uptake greater than the mediastinum but less than the liver
4	Uptake moderately higher than the liver
5	Uptake markedly higher than the liver

Recommendations

FDG-PET is more accurate than CT alone in HL and is therefore recommended for staging and for evaluation of end of treatment responses.

Interim PET scan is now considered a standard of care in the front-line setting. This should be performed after 2 cycles of ABVD (or 3 cycles when following the RAPID approach). Interim FDG-PET should be scheduled as close to the next cycle as possible and no sooner than 10 days after the previous cycle.

The only setting in which interim PET is not mandatory is when 2 cycles of ABVD plus 20Gy IFRT are planned, in which case PET scan can be deferred until after completion of radiotherapy.

Interim PET scans should be reported by an experienced nuclear medicine consultant using the Deauville scale. In general, an interim PET scan demonstrating \geq Deauville 3 uptake should be discussed at an MDT.

End of treatment PET scans should ideally be performed 6-8 weeks, and no sooner than 3 weeks, post-chemotherapy (Cheson, Fisher *et al*, 2014).

PET scans should be performed \geq 3 months post radiotherapy (Cheson, Fisher *et al*, 2014).

4 Delivery of Care

Patients should be managed according to the guidance and recommendations set out by NICE in 2016: Haematological cancers: improving outcomes www.nice.org.uk/guidance/ng47.

4.1 Children, teenagers and young adults

Children below the age of 16 years with a diagnosis of HL or suspected HL must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams.

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYC designated hospital.

5 Patient Information and Support

All patients must have a named key worker. This is usually (but not always) the clinical nurse specialist.

Written and verbal information are essential. The key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

Lymphoma Action (formerly the Lymphoma Association), Bloodwise (formerly Leukaemia & Lymphoma Research) or Macmillan Cancer Support information booklets are good sources of patient information at diagnosis. Patient leaflets are available for all treatment options and are also available for download on the following websites:

www.macmillan.org.uk/information-and-support/lymphoma/lymphoma-hodgkin/understanding-cancer

www.lymphoma-action.org.uk/types-lymphoma/hodgkin-lymphoma

www.bloodwise.org.uk/info-support/lymphoma

6 Treatment Recommendations for Classical Hodgkin Lymphoma (cHL)

All patients should, if appropriate should be offered the opportunity to participate in clinical trials and consideration should be given to referring patients to centres where suitable trials are open. Close collaboration with a clinical oncologist is recommended when planning treatment.

6.1 Early stage cHL

6.1.1 Early stage favourable disease

- Patients with early stage disease and no unfavourable risk factors (GHSG or EORTC; see [section 3.2](#)) generally have excellent outcomes.
- In the GHSG multicentre HD10 trial, 1,190 patients with early stage cHL were prospectively randomised to receive treatment in a 4-way randomisation of 2 versus 4 cycles of ABVD followed by consolidation with either 20Gy or 30Gy of involved field radiotherapy (IFRT). The 8-year freedom from progression and overall survival (OS) rates were 87.1% and 94.5% respectively, with no significant difference between the four arms (Engert, Plutschow *et al*, 2010). On the basis of these results, 2 cycles of ABVD followed by 20Gy IFRT is the standard of care in early stage favourable cHL, excluding cases where radiotherapy carries significant risk.
- In the UK NCRI RAPID study of stage I and IIA non-bulky cHL, patients with a negative interim PET (Deauville score 1-2) after 3 cycles of ABVD were randomised to receive either radiotherapy or no further treatment (Radford, Illidge *et al*, 2015). It should be noted that some non-bulky, early stage unfavourable cHL patients (by GHSG or EORTC criteria) would have been included in this study. Investigators reported reduced 3-year progression-free survival (PFS) with chemotherapy alone compared with chemo-radiotherapy (90.8% versus 94.6%) in PET negative patients, though the lower cut-off of the 95% confidence interval fell just below the nominated 7% non-inferiority margin for the study. Therefore, omission of radiotherapy is associated with a slightly higher risk of relapse even in cases with a negative interim PET and radiotherapy should only be omitted if it is felt to carry a significant risk.
- Early stage favourable cHL patients in the EORTC H10 study were randomised to receive either a standard arm of ABVD x2 and INRT or an experimental arm containing a PET-directed randomisation after 2 cycles of ABVD (Andre, Girinsky *et al*, 2017). In the experimental arm, randomised patients who were PET negative (Deauville score 1-2) went on to receive 2 further cycles of ABVD while PET positive patients received escBEACOPP x2 and INRT. Pre-planned analysis for interim PET negative patients at 1 year reported a PFS of 100% in the standard arm versus 94.9% in the experimental arm. Randomisation to the experimental arm was suspended for interim PET negative patients on the basis of the inferior PFS at 1 year with chemotherapy alone, suggesting a benefit with combined modality treatment in early stage favourable patients.

6.1.2 Early stage unfavourable disease

- In the GHSG HD11 study, 1,395 patients with early unfavourable HL were assigned to either ABVD x4 or BEACOPP x4 (Eich, Diehl *et al*, 2010). This was followed by consolidation with either 20Gy or 30Gy IFRT, resulting in four possible randomisations. There was no

significant difference in OS (94.5% at 5 years) but an inferior PFS was recorded with ABVD x4 and 20Gy IFRT. Greater toxicity was observed in the BEACOPP arms, making ABVD x4 followed by 30Gy IFRT the most attractive among the four arms. It should, however, be borne in mind that greater treatment related toxicity was seen in patients who received 30Gy compared with 20Gy IFRT (12% versus 5.7%).

- The early stage unfavourable patients in the EORTC H10 study were randomised to receive either a standard arm of ABVD x4 followed by involved nodal radiotherapy or an experimental arm containing a PET directed randomisation after 2 cycles of ABVD. In the experimental arm, PET positive patients were switched to 2 cycles of escBEACOPP and INRT, whereas PET negative patients received 4 further cycles of ABVD with no radiotherapy. Similar to the favourable risk cohort, randomisation was closed for the interim PET negative patients following interim futility analysis at 1 year. It should be noted that the difference in PFS between ABVD x4 + INRT and ABVD x6 at 5 years was 2.5% (92.1% versus 89.6% respectively) with no difference in overall survival (Andre, Girinsky *et al*, 2017). ABVD x6 is therefore an effective alternative to ABVD x4 + RT in this cohort and may have an advantage in terms of long term side effects in selected cases.
- Updated results of the EORTC H10 reported a significantly superior 5-year PFS in the combined cohort (favourable and unfavourable) of interim PET positive (Deauville score 3-5) early stage patients treated with escBEACOPP + INRT compared to ABVD + INRT (90.6% versus 77.4% respectively), with a statistically non-significant improvement in OS. However, it should be noted that the majority of patients in this group had unfavourable features (97 favourable versus 264 unfavourable) (Andre, Girinsky *et al*, 2017). Thus, in early stage unfavourable patients, intensification to escBEACOPP x2 + RT is a valid option in the setting of a positive interim PET following 2 cycles of ABVD.

Toxicity considerations

- Combined modality therapy confers a superior PFS in most scenarios of early stage favourable HL but is associated with the potential for late effects including endocrine abnormalities, cardiac morbidity and second cancers. All patients should therefore have the opportunity to be involved in an informed decision-making process together with a clinical oncologist. In certain situations, for example in females below 35 years of age with mediastinal or axillary sites of cHL, additional cycles of chemotherapy without radiotherapy can be considered.
- Despite previous concerns about the gonadotoxicity of BEACOPP, preliminary analysis of the HD 14 trial revealed no significant differences in female fertility potential after 2xescBEACOPP + 2xABVD compared with ABVD x4 (Behringer, Thielen *et al*, 2012, von Tresckow, Plutschow *et al*, 2012). However, the EORTC H10 study reported more grade 3 and 4 hematologic toxicities in the BEACOPPesc + INRT arm compared with the ABVD + INRT arm - neutropenia (53.5% versus 30.3%), anaemia (4.9% versus 0.0%), and thrombocytopenia (19.7% versus 0.0%) respectively. Grade 3 and 4 febrile neutropenia episodes occurred in 23.9% versus 1.1% of patients respectively (Andre, Girinsky *et al*, 2017).
- Patients over 60 years of age are at a higher risk of severe bleomycin lung toxicity if bleomycin is administered beyond 2 cycles of ABVD (Boll, Goergen *et al*, 2013, Boll, Goergen *et al*, 2016). Therefore, omission of bleomycin beyond 2 cycles should be considered in patients over the age of 60 years.

Recommendations for treatment of early stage cHL

- Combined modality therapy reduces the risk of relapse in most cases of early stage HL.
- The suitability of RT in individual cases should be discussed at the MDT in the presence of a clinical oncologist and where appropriate, patients should be referred early for RT.
- Patients with early stage disease should be stratified into favourable and unfavourable risk groups.

Favourable risk – there are 3 options based on the risk stratification employed

- In cases with no B-symptoms or bulk disease, 3 cycles of ABVD without RT (RAPID approach) can be considered.
- If applying the GHSG criteria, 2 cycles of ABVD followed by 20Gy RT should be considered if RT is suitable. If RT is not suitable, 3 cycles of ABVD as per the RAPID approach can be considered.
- If applying EORTC criteria, 2 cycles of ABVD followed by 20Gy RT is recommended only for those with a 'negative' interim PET scan after 2 cycles. See below for patients with a positive interim PET scan.

Unfavourable risk – there are 3 options based on the risk stratification employed

- In stage II cHL with B-symptoms or bulk, the RATHL protocol for advanced cHL can be considered (nearly 40% of patients in the RATHL study fell into this category).
- If applying the GHSG criteria, ABVD x4 followed by 30Gy RT should be considered. In patients unsuitable for radiotherapy, ABVD x6 with a RATHL-based approach can be considered.
- If applying EORTC criteria, all patients should receive 2 cycles of ABVD followed by an interim PET scan. Further treatment is dictated by the result of the scan, as below.

Early stage unfavourable patients with a 'negative' interim PET (Deauville score 1-2)

- 2 further cycles of ABVD followed by 30Gy RT, if radiotherapy is suitable.
- 4 further cycles of AVD if radiotherapy is not suitable, i.e. follow RATHL approach.

Early stage patients with a 'positive' interim PET (Deauville score 3-5), favourable or unfavourable risk

- Assess suitability for intensification to escBEACOPP x2 + 30Gy RT.

6.2 Treatment of advanced stage cHL (including stage II disease with B-symptoms or bulk)

In advanced stage cHL, a number of trials using ABVD have shown a failure-free survival of 73–83% with OS in the range of 82–95% (Follows, Ardeshtna *et al*, 2014). The best results have been reported in the RATHL trial but it should be noted that other international trials have not included patients with stage II disease (in the RATHL trial, 41.6% of patients had stage IIb disease or stage IIa with adverse risk factors) which may account in part for the good overall outcomes achieved in this trial (Johnson, Federico *et al*, 2016).

Until recently, the standard of care for management of advanced stage HL in the UK was 6-8 cycles of ABVD or 6 cycles of escBEACOPP (Follows, Ardeshtna *et al*, 2014). Recent publication of the RATHL trial has led to a standardisation in treatment of most patients with advanced stage disease.

- In the RATHL trial, 1,214 patients with advanced stage cHL (including stage IIb and IIa with adverse features) were treated with 2 initial cycles of ABVD followed by an interim PET (iPET) scan.
- A Deauville score of 1-3 was considered negative, a score of 4-5 was positive.
- 84% of patients had a negative PET scan after ABVD x2.
- 16% of patients had a positive PET scan after ABVD x2.
- Patients with negative PET were randomised to 4 further cycles of ABVD or 4 cycles of AVD – omitting bleomycin from subsequent cycles.
- With a median follow-up of 41 months, there was no significant difference in PFS or OS between the two cohorts, and significantly lower toxicity in the AVD arm.

Table 5: PFS and OS in patient with negative interim PET in the RATHL trial

	ABVD	AVD
3yr PFS	85.7%	84.4%
3yr OS	97.2%	97.6%

- It is therefore now appropriate to omit bleomycin from subsequent cycles of chemotherapy for patients with a negative interim PET scan (Deauville score 1-3) after 2 cycles of ABVD.
- Patients who had a positive interim PET scan (Deauville score 4-5) after 2 cycles of ABVD (n=182), received 4 cycles of BEACOPP (either escBEACOPP or BEACOPP-14 according to centre preference). The subsequent PET scan was negative in 74% of these patients. Note that patients with positive interim PET were not randomised to intensification versus continuing with ABVD, all patients with a positive interim PET went on to receive intensified therapy.
- The PFS and OS for interim PET positive patients were 67.5% and 87.8%, and although there was no randomisation to intensification versus continuing ABVD, the good outcome in this group of patients validates the option of intensification to BEACOPP if PET positive after 2 cycles of ABVD.
- There was an indication that patients with Deauville score 5 on interim PET had a poor outcome despite intensification to BEACOPP (20/38 treatment failures, 53%) suggesting that these patients may require up-front salvage therapy.
- Radiotherapy in the RATHL trial was at the investigators' discretion and was administered to 3.5% of PET negative patients and 6.5% of patients in the entire trial. In PET negative patients, neither disease bulk nor PET score (Deauville score 1-3) were associated with relapse, indicating that omitting radiotherapy in patients who are PET negative, regardless of original disease bulk or residual masses, may be acceptable. However, this was not assessed in a randomised manner and radiotherapy to sites of initial disease bulk needs to be decided on a case-by-case basis.

It is important to note that 15% of patients with a negative interim PET treated on the RAHTL trial subsequently progressed within 3 years, suggesting the negative predictive value of interim PET is therefore lower than was previously thought. Disease bulk and level of remission (Deauville score 1-3) did not predict relapse, but IPS score and stage were associated with relapse. This may reflect the low use of RT in this trial, hence the need to consider RT to sites of initial bulk on a case-by-case basis.

There has been much debate about the choice of induction chemotherapy regimen with apparently superior failure-free survival with the German escBEACOPP approach with which few patients require radiotherapy.

In the GHSG HD9 trial, significant improvements in both failure-free and overall survival were achieved with 8 cycles of BEACOPP (baseline or escalated) compared to 8 cycles of alternating COPP/ABVD (Engert, Diehl *et al*, 2009).

Although there was significantly greater toxicity in the BEACOPP arms, the improvements in failure-free and overall survival prompted many to adopt this approach in the first line management of advanced stage cHL.

The GHSG HD12 trial demonstrated that the toxic effects of 8 cycles of escBEACOPP could be attenuated by using escBEACOPP for 4 cycles followed by baseline BEACOPP for 4 cycles (BEACOPP₄₊₄) with no apparent loss in efficacy (Borchmann, Haverkamp *et al*, 2011). Subsequently, it was demonstrated in the HD15 trial that consolidation radiotherapy could be safely omitted after BEACOPP in patients who had a negative FDG-PET scan after 6 cycles of BEACOPP (Engert, Haverkamp *et al*, 2012).

BEACOPP has not been widely adopted in the UK due to concerns about toxicity and the practicalities of delivering this dose-intense regimen compared to ABVD. Furthermore, recent studies have failed to support the original data from HD9. Two Italian studies have demonstrated improved EFS with BEACOPP compared to ABVD but no OS benefit (Federico, Luminari *et al*, 2009, Viviani, Zinzani *et al*, 2011). There were criticisms of these trials, but a large, well-conducted international study, the EORTC 20012 trial, has found similar findings. In this trial of patients with advanced stage cHL and high International Prognostic Score (≥ 3), there was a marginal improvement in DFS and PFS with BEACOPP₄₊₄ compared to 8 ABVD but no significant difference in 4-year EFS or OS (Carde, Karrasch *et al*, 2016).

Recent publication of the HD18 study in abstract form at EHA 2017 adds further weight to the consideration of escBEACOPP in the first line therapy of advanced stage cHL (Borchmann 2017). In this study it was demonstrated that an estimated 5-year PFS of $>90\%$ could be achieved by limiting treatment to 4 cycles of escBEACOPP in those achieving a negative PET scan (defined as uptake lower than in the mediastinum) after 2 cycles. Given that approximately 50% of patients were PET negative at this timepoint, this approach represents an attractive option, delivering excellent OS and lower toxicity than 6-8 cycles of escBEACOPP.

Previously, some reserved BEACOPP for those with high risk disease identified by IPS score. However, this approach has not been assessed prospectively. There is no evidence to support a particular cut-off above which BEACOPP may be more beneficial than ABVD. Recent data from the EORTC 20012 trial indicates that there is no benefit of BEACOPP over ABVD in patients with IPS score of ≥ 3 (Carde, Karrasch *et al*, 2016).

Given the improved disease control and lower rate of RT in patients treated with escBEACOPP, it is reasonable to consider this more intensive option in certain patients, for example those with extensive bulky disease in whom RT fields would be too extensive to deliver consolidation RT.

If escBEACOPP is used, it should be delivered as per HD18 with an interim PET scan after 2 cycles and limiting treatment to 4 or 6 cycles depending on response. Radiotherapy can usually be omitted if PET negative after BEACOPP.

When considering first-line treatment, note that salvage is successful in many patients relapsing after ABVD and that there may be a lower response to salvage after BEACOPP (Viviani, Zinzani *et*

al, 2011). Further analysis of the EORTC 20012 trial is anticipated to report on success of salvage after BEACOPP compared to ABVD. Additionally, if BEACOPP is used upfront, patients must be made aware of the increased risk of serious toxicities and late effects including secondary malignancies and sub-fertility compared to ABVD. BEACOPP regimens should not be used in patients aged over 60 years due to unacceptable toxicities (Engert, Diehl *et al*, 2009).

ABVD should be delivered on schedule with infusions given every 14 days irrespective of neutropenia, particularly when this is isolated. Granulocyte colony-stimulating factor (G-CSF) is required only for patients with infectious complications. We recommend GCSF prophylactically after infections requiring hospital admission.

Recommendations

- Most patients with advanced stage cHL should be treated with 2 cycles of ABVD followed by interim PET scan.
- If PET negative (Deauville score 1-3), de-escalation of chemotherapy to AVD (i.e. omission of bleomycin) is recommended for the subsequent 4 cycles of chemotherapy.
- Where there is disease bulk at baseline, consideration should be given to consolidation RT on a case-by-case basis if complete metabolic remission is achieved. Most patients without disease bulk at baseline who achieve PET negativity will not require RT.
- It should be noted that the negative predictive value of interim PET is not 100%, and 15% of patients with a negative interim PET scan progressed within 3 years in the RATHL trial.
- If interim PET scan is positive (Deauville score 4-5), intensification to BEACOPP14 or escBEACOPP should be considered for 4 cycles, with a further PET scan after 2 cycles to ensure that there is response.
- Patients with D5 on interim PET appear to have poor outcomes with BEACOPP and consideration should be given to salvage regimens in these patients (rather than intensifying to BEACOPP).
- It is recognised that BEACOPP may be a more effective first line therapy, but it is not clear who benefits from this more intensive regimen with higher toxicities and costs than ABVD – patients treated with this approach must be fully appraised of the risks and benefits. Patients with a high burden of disease, including sites of bulk that would require extensive RT fields, may benefit most from this approach.

6.3 Radiotherapy techniques

Radiation techniques have evolved significantly in the last 30 years. Radiation fields have become progressively and significantly smaller and, in more recent years, there has been increasing use of advanced radiotherapy planning techniques, such as intensity-modulated radiotherapy (IMRT). Whilst some European trials such as H10 (Andres *et al*, 2017) use involved-nodal radiotherapy (INRT), the prerequisite for this is a pre-chemotherapy PET/CT immobilised in the radiotherapy position. An internationally accepted alternative to this is involved-site radiotherapy (ISRT) where only the involved nodes are treated but with a more generous margin allowed for variations in the patient positioning between imaging data (Specht *et al*, 2014, Hoskin *et al*, 2012). The UK standard is now ISRT rather than involved-field radiotherapy (IFRT). Radiotherapy planning techniques chosen will be dependent on patient-related factors such as age, gender and disease distribution. IMRT or motion management techniques such as 4D-CT or deep-inspiratory breath-hold techniques should be considered wherever significant normal tissue sparing will be achieved with advanced planning modalities.

Radiotherapy Doses

Early Stage Favourable (GHSG criteria)	20Gy in 10 fractions
Early Stage Unfavourable	30Gy in 15-17 fractions
PET negative previous sites of disease bulk or residual disease	30Gy in 15-17 fractions
PET positive sites of residual disease	30Gy in 15-17 fractions, or 36Gy in 18-20 fractions, or 40Gy in 20-22 fractions

6.4 Treatment of cHL in special circumstances**6.4.1 Elderly patients**

- Old age is recognised as an independent adverse prognostic factor for cHL. In a retrospective multicentre study, the 5-year survival for patients over the age of 60 was estimated at 58% (Evens, Helenowski *et al*, 2012).
- Increased toxicity and treatment-related mortality have been observed in patients aged over 60 years treated with ABVD, compared with patients aged less than 60 years. This includes increased incidence of neutropenia, infections and bleomycin-induced lung toxicity (BLT) (Evens, Helenowski *et al*, 2012, Boll, Goergen *et al*, 2013). BLT occurred in 43% of patients over 60 years receiving ABVD in the latter study, with associated mortality of 18%.

In an analysis by Boll *et al* of patients over 60 years of age treated on the GHSG HD10 and HD13 trials for early stage cHL, a high risk of severe toxicity (7/69 patients with 3 lethal events) was seen in patients who received 4 cycles of ABVD compared to those who received 2 cycles in whom toxicity was rare. The difference in 5-year freedom from treatment failure between ABVD and AVD in the HD13 study was 3.9% (95% CI 7.7 to 0.1%) (Boll, Goergen *et al*, 2016). Therefore, in patients over 60 years of age receiving ABVD for early stage cHL, bleomycin should be avoided beyond 2 cycles, or omitted altogether.

- The SHIELD study in the UK evaluated VEPEM-B in the treatment of 103 patients over the age of 60. In 31 patients with early stage disease (VEPEM-B x3 and radiotherapy), the 3-year PFS and OS were 74% and 81% respectively. In patients with advanced stage HL (N=72, VEPEM-B x6), 3-year PFS and OS were 58% and 66% respectively (Proctor, Wilkinson *et al*, 2012). Of note, frail patients were excluded from this study.
- The non-anthracycline containing regimen ChIVPP is another option in elderly patients or in those unable to have anthracyclines. Failure-free survival at 5 years ranged from 51% to 75% depending on stage. However, response rates in patients over 50 years of age were not very encouraging (1995).
- There is a need for clinical trials specifically addressing the treatment of HL in older patients. Where clinical trial entry is not available, treatment recommendation is according to performance status, cardiac and respiratory assessment, and patient preference.

6.4.2 Pregnancy

- There is very limited evidence for management of cHL in pregnancy. Some case reports, case series and reviews have been published on this subject (Bachanova and Connors, 2008, Follows, Ardeshtna *et al*, 2014, Eyre, Lau *et al*, 2015).
- HL in pregnancy should always be managed in conjunction with an obstetrician experienced in high-risk pregnancy.
- In some cases, it may be possible to delay treatment until after delivery, but this should be done with caution.
- MRI and ultrasound can be used for staging and response assessment to avoid X-ray exposure.
- ABVD is the treatment of choice in this situation. As far as possible, chemotherapy exposure should be avoided in the first trimester as the risk to the developing foetus is theoretically at its highest.
- Radiotherapy should be delayed until after delivery wherever possible.

6.4.3 HIV

- HIV-positive patients have more extensive disease and adverse prognostic features compared with HIV-negative patients.
- Standard management with ABVD combined with antiretroviral therapy can achieve responses approaching those seen in the HIV-negative population (Montoto, Shaw *et al*, 2012).
- Stage and risk-adapted treatment is both feasible and effective in this group of patients in the era of highly active antiretroviral therapy (Hentrich, Berger *et al*, 2012).

6.5 Management of relapsed or refractory cHL

All patients with relapsed or refractory disease should, if appropriate, be offered the opportunity to participate in clinical trials and consideration should be given to referring patients to centres where suitable trials are open.

The key recommendations below have been adopted from the BCSH guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma with some modifications based on more recent data (Collins, Parker *et al*, 2014).

Repeat biopsy is generally recommended in patients thought to have relapsed and should be considered in those who have residual FDG-avid lesions post-therapy.

In patients who are fit for intensive therapy, the standard of care at first relapse is to deliver salvage therapy and consolidate remission with an autologous stem cell transplant. In patients who are not fit for high dose therapy alternative approaches need to be adopted.

6.5.1 Salvage therapy for relapsed cHL in patients fit for intensive therapy

- The choice of first-line salvage regimen in patients who are fit enough for autologous stem cell transplantation (autoSCT) should be based on patient factors and the familiarity of the treatment centre with the regimens. A platinum-based regimen is usually recommended, e.g. ESHAP, DHAP, GEM-P, or ICE. IGEV can be considered as an alternative.

- If ASCT is planned, regimens containing stem cell toxic agents (such as carmustine and melphalan) should be avoided until stem cells have been successfully harvested.
- In the rare event of late relapse >5 years after primary therapy occurring at a localised site without B-symptoms, treatment with standard-dose chemotherapy and IFRT alone, without consolidating with autoSCT, may be appropriate.
- It is standard practice to re-stage with PET-CT after 2 cycles of salvage chemotherapy unless there is clinical evidence of poor response or progression before this.
- The aim of salvage treatment should be to achieve an FDG-PET-negative remission (complete metabolic remission).
- AutoSCT is the standard treatment for patients with relapsed or primary resistant disease who achieve a complete response to first-line salvage therapy. The 5-year PFS for patients undergoing autoSCT in CR is approximately 70% (Collins, Parker *et al*, 2014).
- Choice of conditioning regimen should be based on familiarity of the treatment centre with the regimen.
- AutoSCT is not recommended in those failing to achieve an adequate response.

6.5.2 Treatment of patients not responding to first-line salvage

- For patients who fail to respond to conventional combination salvage regimens, consider switching to brentuximab (alone or in combination with bendamustine) or an alternative non-cross-resistant salvage regimen.
- Brentuximab vedotin (BV) is currently accessible through the Cancer Drugs Fund for relapsed CD30+ HL following at least two prior therapies, for patients in whom autoSCT or multi-agent chemotherapy regimens can't be delivered. Of note, patients who received BV upfront as part of the ECHELON-1 study are eligible for re-treatment if they meet the above criteria.
- There is limited data to show that brentuximab in combination with bendamustine is a highly efficacious regimen deliverable in the outpatient setting, with 90% CR rate after 2-6 cycles reported in a small study (Kalac, Lue *et al*, 2016).
- Re-staging with PET-CT should be performed after 4 cycles of treatment with BV or other regimens. BV should be discontinued after 4 cycles unless a PR or CR is achieved.
- A maximum of 16 cycles of brentuximab can be given.
- In the era of PET re-staging, it is not clear whether the number of lines of treatment taken to achieve complete metabolic remission influences outcome with autoSCT. Available evidence supports the concept that patients who achieve complete metabolic remission after one or two lines of salvage have similar outcomes. It is probable that those achieving such responses after further lines of salvage have incrementally inferior outcomes with autoSCT, particularly those with extranodal disease.
- There is compelling evidence from early stage clinical trials that immune checkpoint blockade inhibition with PD1 inhibitors such as nivolumab and pembrolizumab is a highly effective treatment strategy in patients with relapsed or refractory cHL, even in those previously treated with brentuximab (Ansell, Lesokhin *et al*, 2015, Chen, Zinzani *et al*, 2017). It is anticipated that these agents will soon change the management of relapsed/refractory cHL.

- Patients who have not achieved a complete remission but have non-progressive, chemo-sensitive disease should not proceed to autoSCT. Such patients should be considered for allogeneic SCT.

6.5.3 Treatment of relapse post autoSCT

- Patients relapsing after autoSCT can be considered for treatment with brentuximab vedotin – provided they meet the criteria described above in section 6.5.2. Note that re-treatment is permitted in patients who have previously achieved at least a PR with this agent, provided that the cumulative total number of doses does not exceed 16.
- The PD1 inhibitor nivolumab has recently been approved for use in the relapsed setting after autoSCT in those who have previously been treated with BV.
- In patients relapsing after autoSCT who have chemo-sensitive disease, allogeneic SCT should be considered.

6.5.4 Role of allogeneic stem cell transplantation in relapsed or refractory cHL

- Allogeneic transplantation using a reduced intensity conditioning regimen is the treatment of choice for patients who relapse after autoSCT and have chemo-responsive disease.
- Allogeneic transplantation using a reduced intensity conditioning regimen should be considered for patients who fail to achieve complete remission with salvage chemotherapy but have non-progressive, chemo-sensitive disease.
- An appropriately human leukocyte antigen- (HLA-) matched unrelated donor should be considered when there is no HLA-matched sibling.
- Investigation of the use of allogeneic transplantation earlier in the treatment pathway should – where possible – be performed in the context of prospective clinical trials.

6.5.5 Management of relapsed cHL in patients not fit for intensive therapy

In patients not considered to be fit enough for high-dose therapy and autoSCT there is no standard of care. Options for treatment in this situation include:

- In patients meeting the criteria for BV as described above in section 6.5.2, single agent BV for a maximum of 16 cycles can be considered.
- Combined modality therapy, especially in early stage relapse and in patients who have not received prior radiotherapy or who have relapsed outside the initial radiotherapy field.
- Salvage radiotherapy alone may be considered in selected patients not eligible for autoSCT, with limited stage disease at relapse.
- In patients unlikely to tolerate the toxicities associated with more intensive regimens, palliation with either a single agent or with a multi-agent oral regimen with or without intravenous vinblastine should be considered.

7 Bleomycin Lung Toxicity

Bleomycin lung toxicity (BLT) is a disabling side effect of therapy of HL and is associated with a significant mortality risk. In a retrospective analysis of 141 patients receiving bleomycin-based chemotherapy for HL, 18% developed BLT (Martin, Ristow *et al*, 2005). In this study, an association was found with increasing age and the use of GCSF. Mortality in those who developed lung toxicity was 24%.

The following measures should be taken to minimise the risk of this serious complication:

- Regular clinical assessment for respiratory symptoms such as a dry cough or exertional dyspnoea in patients on bleomycin-based therapy and low threshold for investigation with HRCT and lung function tests in those who develop these symptoms.
- Bleomycin therapy should be withheld if the pulmonary diffusion capacity for carbon monoxide (DLCO) falls to 30-35% of initial value, if the forced vital capacity (FVC) falls significantly, or if there are any clinical or radiographic features indicating pulmonary toxicity.
- Consider omission of bleomycin after cycle 2 of ABVD in patients with advanced stage disease achieving CMR after 2 cycles and in early stage disease for patients over 60.
- Omission of regular GCSF in treatment protocols containing bleomycin wherever possible.

If BLT is suspected or confirmed, bleomycin should be stopped and the patient promptly referred to a respiratory physician. Early initiation of corticosteroid can prevent progression of bleomycin pneumonitis to fibrosis but is of questionable value once fibrosis has set in.

8 Supportive Care

Supportive care is very important for all patients with haematological malignancies.

Clean, neutropenic diets should be instituted and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols, with antibiotic choice largely dependent on local microbiological flora.

8.1 Transfusions

All patients with cHL should receive irradiated blood products indefinitely from diagnosis onwards.

9 End of Treatment Information

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary. On successful completion of treatment, both the patient and their GP should be made aware of follow-up plans and potential future disease or treatment-related issues.

9.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of their treatment.

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. The aim is to provide information not only to the patient but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information. The treatment summary should be completed by the named clinical nurse specialist/key worker with the patient and a copy sent to the GP and the patient.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

Recommendation

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary.

Lymphoma team, key worker and patient support group contact details should be reiterated and details of future follow-up arrangements provided.

Patients should be educated regarding the potential symptoms and signs that might indicate disease progression or recurrence and counselled on the need to re-present to the unit should these occur.

People should be offered access to a health and wellbeing event at the end of treatment. This should provide information to enable a person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including diet and physical activity.

The MDT outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment with the GP.

10 Follow-up Arrangements

Routine surveillance imaging is not recommended.

The nature and frequency of follow-up review and investigations will be tailored by presentation, treatment type, treatment toxicities, disease-related effects, co-morbidities and psycho-social factors.

Standard follow-up arrangements are to review patients every 3 months for the first year.

Follow-up thereafter may be conducted according to local practice. In some centres, patients are transferred to the self-management pathway one year after completion of therapy. Routine review is then not conducted and is instead precipitated at a patient's request.

All patients should be made aware of the risks of secondary cancers and participate in national cancer screening programmes, and should be made aware of the increased risk of cardiovascular disease.

Patients who have had radiotherapy as part of their treatment will require different follow-up plans to those who have not, e.g. annual thyroid function tests are required if the neck was irradiated, and early referral to the breast cancer screening programme in women who received radiation to breast tissue.

11 Research and Clinical Trials

All patients should be entered into clinical trials and tissue stored where possible. Ideally, all patient diagnostic material should be bio-banked in an ethically approved research framework.

12 Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

The key recommendations in this section have been adopted from the 2016 BCSH guideline on the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma (McKay, Fielding *et al*, 2016).

NLPHL is a rare disease accounting for 3–8% of all Hodgkin lymphoma (HL). Peak incidence is in adolescents aged 13-14 and adults aged 30-35yrs. It is clinically, pathologically and prognostically distinct from classical HL. Most patients (~70%) present with early stage, non-bulky nodal disease and have a 10-year overall survival of >80%. Late and multiple relapses are well recognised. There is a risk of transformation (up to 30% at 20 years) (Al-Mansour, Connors *et al*, 2010) to diffuse large B-cell lymphoma (DLBCL) with a median time to transformation of approximately 8 years.

12.1 Essential investigations

Work up is as for cHL (see [section 3: Investigation and Diagnosis](#)). Of note, unlike cHL there is no evidence to support the use of interim PET or CT to guide treatment in NLPHL.

12.2 Front-line treatment of adult NLPHL

12.2.1 Early stage IA and IIA

Surgical excision is recommended in those with localised, resectable disease. Patients with residual but localised NLPHL (stage IA and IIA with ≤ 2 sites of disease) should be offered involved field radiotherapy (IFRT) (1B). A watch and wait approach may be considered in patients who are in complete remission following excision after discussion with a radiation oncologist.

Patients with stage IIA who are not suitable for IFRT alone (>2 sites of disease or extensive stage II infra-diaphragmatic disease with close proximity to radiosensitive organs such as kidney, bowel and pancreas) should be treated as advanced stage disease.

12.2.2 Stages IIB, III and IV

Always consider the possibility of high-grade transformation in patients with rapidly progressive disease, marked B symptoms, focal abnormalities in the spleen or bone marrow involvement. An additional tissue biopsy is justified in these patients.

Consider whether treatment is immediately necessary or whether a period of watch and wait would be appropriate.

Consider R-CVP/R-CVinbP/R-ABVD in patients requiring combination chemotherapy.

Consider R-CHOP in patients with evidence (or a high index of suspicion) of transformed disease.

Consider rituximab monotherapy in patients with advanced stage NLPHL who have serious co-morbidities that would preclude the use of combination chemotherapy.

There is no evidence to support rituximab maintenance for patients responding to first-line therapy.

12.3 Treatment of relapsed NLPHL

Repeat biopsy is advised to exclude high grade transformation.

Consider radiotherapy for an isolated local recurrence especially at a site of previous excision.

Consider a watch and wait approach for asymptomatic patients with advanced stage disease.

Offer chemotherapy for patients with symptomatic advanced stage disease at relapse.

Consider rituximab monotherapy in those patients who require therapy and whose co-morbidities preclude the use of combination chemotherapy.

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<http://www.hmrn.org/statistics>

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