bjh guideline

Guidelines for the management of diffuse large B-cell lymphoma

Sridhar Chaganti,[1] Tim Illidge,[2] Sally Barrington,[3] Pam Mckay,[4] Kim Linton,[5] Kate Cwynarski,[6] Andrew McMillan,[7] Andy Davies,[8] Simon Stern,[9] Karl Peggs[10] and on behalf of the British Committee for Standards in Haematology

[1]Department of Haematology, Queen Elizabeth Hospital, Birmingham, [2]Department of Clinical Oncology, Christie Hospital, Manchester, [3]PET Imaging Centre, King's College London, King's Health Partners, St. Thomas' Hospital, London, [4]Department of Haematology, West of Scotland Cancer Centre, Glasgow, [5]Department of Medical Oncology, Christie Hospital, Manchester, [6]Department of Haematology, Royal Free Hospital, London, [7]Department of Haematology, City Hospital, Nottingham, [8]Department of Medical Oncology, Southampton General Hospital, Southampton, [9]Department of Haematology, St Helier Hospital, Carshalton, and [10]Department of Haematology, University College Hospital, London, UK

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Scope

This guideline is aimed at providing healthcare professionals with clear guidance on the management of patients with diffuse large B-cell lymphoma (DLBCL). Disease confined to specific extranodal sites, such as primary central nervous system lymphoma, testicular lymphoma, primary mediastinal large B-cell lymphoma, DLBCL of leg type, etc., is beyond the scope of this guideline. It is not the intention of this guideline to provide treatment recommendations for all situations and clinicians are advised to make management decisions taking into account individual patient circumstances.

Methodology

The guideline group was selected to be representative of UK experts in the assessment and treatment of DLBCL. Recommendations are based on a systematic review of published English language literature up to January 2015. MEDLINE database was searched using the key words DLBCL, treatment, radiotherapy and transplant. References from relevant publications were also searched. Other published guidelines, including the US National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines, were also noted.

The writing group produced a draft guideline. Review of the manuscript was performed by the British Committee for Standards in Haematology (BCSH) by the Haemato-oncology sounding board of the British Society for Haematology (BSH). This consists of 50 or more members of the BSH who have reviewed this Guidance and commented on its content and applicability in the UK setting. It has also been reviewed by a patient representative nominated by the Lymphoma Association, but the Association does not necessarily approve or endorse the contents.

Recommendation grading

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified on the BCSH web site. (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and the GRADE working group website (http://www.gradeworkinggroup.org/index.htm).

Background

This is a new evidence-based guideline on behalf of the BCSH for the management of diffuse large B-cell non-Hodgkin lymphoma following a primary systematic review of the evidence by the writing group using the methodology described above.

Introduction

Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma (NHL), accounting for 30–40% of all cases (Rodriguez-Abreu *et al*, 2007). Although most patients are cured with 6–8 cycles of R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy, about 10–15% have primary refractory disease and a further 20–30% relapse. The

Correspondence: Dr Sridhar Chaganti c/o BCSH Secretary, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
E-mail: bcsh@b-s-h.org.uk

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outlook for non-responders to R-CHOP is poor, though a significant minority can be cured by high dose chemotherapy (HDT) and haemopoietic stem cell transplantation. There is an urgent need to improve outcome for patients with DLBCL.

Baseline investigations and staging

Surgical excisional or incisional biopsy is strongly recommended to obtain adequate tumour tissue for diagnosis. Where this is not possible, core needle biopsies offer an alternative but frequently yield small and insufficient samples for diagnostic confirmation. Fine needle aspiration (FNA) is strongly discouraged. It is recommended that all diagnostic material be reviewed by an expert haematopathologist with clinicopathological correlation in the multidisciplinary team (MDT) setting. All patients should have baseline blood tests, including lactate dehydrogenase (LDH) and screening for human immunodeficiency virus (HIV), hepatitis B and hepatitis C. Left ventricular function should be assessed by echocardiogram or multigated acquisition scan in patients aged >65 years, and those with a cardiac history. Fertility-preserving treatments, such as sperm cryopreservation for male and referral to a fertility specialist in female patients, should be considered for eligible patients.

Staging investigations

A full contrast enhanced staging computerized tomography (CT) scan to include neck, chest, abdomen and pelvis should be performed in all cases. Magnetic resonance imaging (MRI)/CT imaging of the brain, orbits and sinuses will be required for patients with CNS or craniofacial disease. Diagnostic lumbar puncture for cerebrospinal fluid (CSF) analysis, including cytology and flow cytometry, is recommended for patients with suspected CNS involvement. Intrathecal methotrexate should be administered at the same time. A staging positron emission tomography (PET)/CT is strongly recommended as PET is more sensitive, especially for extranodal disease and improves staging accuracy and subsequent response assessment (Meignan *et al*, 2009; Barrington *et al*, 2010, 2014; Quarles van Ufford *et al*, 2010; Cheson *et al*, 2014).The role of a routine staging bone marrow biopsy (BMB) is under scrutiny as PET scanning demonstrates utility for identifying bone marrow involvement (BMI). This is usually seen as unifocal or multifocal uptake, with diffuse activity being less common. In a recent meta-analysis involving 654 patients with aggressive NHL, the pooled sensitivity and specificity for BMI was 89% and 100% respectively (Adams *et al*, 2014). In DLBCL, some studies suggest that PET is more sensitive for BMI than BMB (Berthet *et al*, 2013; Khan *et al*, 2013; Cerci *et al*, 2014), although low volume disease of <10–20% and discordant BMI with a low grade lymphoma may be missed (Paone *et al*, 2009). As low level (<10%) BMI with aggressive lymphoma is unlikely to affect prognosis (Campbell *et al*, 2006), the value of a staging BMB in DLBCL is currently a topic of hot debate. A BMB may nevertheless be required for patients where the presence of discordant BMI with low grade disease will affect management.

Recommendations

- **Wherever possible a surgical excisional or incisional biopsy is strongly recommended to establish diagnosis. Where this is not possible, a core needle biopsy is a less preferred alternative (1A).**
- **All patients should have blood tests including LDH, HIV and hepatitis B and hepatitis C virus screening (1A).**
- **Staging CT of neck, chest, abdomen, and pelvis should be performed for all patients and imaging of the brain, orbits and sinuses in selected patients (1A). Where possible, a staging PET/CT scan is recommended for all patients (1B).**
- **Perform CSF for cytology and flow cytometry in all patients with suspected CNS disease with administration of intrathecal methotrexate at the same time (1A).**
- **Currently a staging bone marrow biopsy remains the standard of care (1A). However, emerging evidence suggests PET may be very valuable in assessing bone marrow involvement in DLBCL though it may miss low level or discordant disease (2B).**
- **All cases should be discussed at a Haemato-oncology MDT meeting, with all diagnostic material being reviewed by an expert haematopathologist (1A).**

Prognostic factors

Clinical prognostic markers predicting adverse outcome include advanced Ann Arbor stage, high International Prognostic Index (IPI) and bulk disease with a tumour diameter of >7·5 cm (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993; Pfreundschuh *et al*, 2008a). The revised IPI (Sehn *et al*, 2007) confirms the prognostic significance of IPI in the R-CHOP era. The recently reported enhanced NCCN-IPI (Zhou *et al*, 2014), appears to better discriminate low and high risk groups. A high IPI also identifies patients at increased risk of CNS disease, which confers poor prognosis.

Gene expression profiling (GEP) identifies distinct DLBCL subtypes, originating from either germinal centre (GCB) or activated B-cells (ABC) (Rosenwald *et al*, 2002). GEP of ABC-type predicted an inferior outcome in the CHOP era (Staudt, 2003). Although R-CHOP improves outcomes in both subtypes, DLBCL of ABC-type continues to have a worse prognosis (on univariate analysis) with a 40% 3-year progression-free survival (PFS) compared to 75% for the GCB-type (Lenz *et al*, 2008). Several immunohistochemistry

(IHC) algorithms (Hans *et al*, 2004; Choi *et al*, 2009; Meyer *et al*, 2011) have attempted to reproduce the GEP classification with good correlation, but the resultant prognostic value has been inconsistent in patients treated with rituximab in addition to chemotherapy (Culpin *et al*, 2013).

MYC rearrangements, found in 5–10% of DLBCL by fluorescent *in-situ* hybridization (FISH) (Obermann *et al*, 2009), confer a poor prognosis in R-CHOP treated patients (Savage *et al*, 2009; Barrans *et al*, 2010). Additionally, some patients have *BCL2* and/or *BCL6* rearrangement (double- or triple-hit lymphomas), also associated with a worse prognosis. Double-hit lymphomas (DHLs) tend to be clinically aggressive with a median survival of <12 months (Aukema *et al*, 2014; Li *et al*, 2014). Recent evidence suggests that the *MYC* partner gene is important; translocation to non-immunoglobulin (Ig) partner genes has little or no impact on survival (Pedersen *et al*, 2014). MYC and BCL2 protein overexpression as detected by IHC is much more common, occurring in 20–30% of DLBCL. This too confers an adverse prognosis with 5-year survival of <30–40% with R-CHOP (Green *et al*, 2012; Johnson *et al*, 2012; Hu *et al*, 2013). Unlike DHLs, which are usually of GCB-type, these tumours tend to be ABC-type. *TP53* mutation and TP53 over expression are associated with decreased survival in both GCB and ABC tumours (Xu-Monette *et al*, 2012). The influence of other biological markers (such as BCL2, BCL6, Ki-67) on survival in the rituximab era is controversial.

Recommendations

- **International Prognostic Index should be calculated for all patients (1B).**
- **Where feasible, all cases of DLBCL should be tested for *MYC* rearrangement by FISH and, if detected, further testing should be performed for *BCL2* and *BCL6* rearrangements (1B).**

Early stage disease

Patients with early stage DLBCL (stage IA or IIA disease) are treated variably with either full course chemotherapy or abbreviated chemotherapy with or without radiotherapy. In the pre-rituximab era, the Southwest Oncology Group study (SWOG 8736) showed that in localized aggressive NHL, combined modality treatment with 3 cycles of CHOP followed by involved field radiotherapy (IFRT) produced superior 5-year PFS (77% vs. 64%) and overall survival (OS) (82% vs. 72%) compared to 8 cycles of CHOP (Miller *et al*, 1998). However, this difference was lost with longer follow-up, suggesting that 3 cycles of chemotherapy may be inadequate for some patients with early stage disease. A British Columbia Cancer agency (BCCA) study showed 5-year OS of 95% with 3 cycles of CHOP plus IFRT in young patients with limited stage DLBCL and no adverse factors (Shenkier *et al*, 2002), further establishing this as an effective strategy. The Eastern Co-operative Oncology Group study (ECOG 1484) randomized complete responders after 8 cycles of CHOP to receive IFRT (30 Gy) or to observation alone and demonstrated an improvement in 6-year PFS with IFRT (73% vs. 56%) (Horning *et al*, 2004).

The Groupe d'Etude des Lymphomes d'Adulte (GELA) performed a randomized study of elderly patients with limited stage disease and low risk IPI (GELA LNH 93-4). There was no benefit from adding radiotherapy to 4 courses of CHOP chemotherapy (Bonnet *et al*, 2007). In young patients (<60 years) with limited stage disease, the GELA LNH 93-1 study demonstrated a 5-year OS advantage for the intensive ACVBP/MIA (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone/methotrexate, ifosfamide, cytarabine) chemotherapy regimen over 3 cycles of CHOP and 40 Gy IFRT(Reyes *et al*, 2005). However, this study included patients with bulk disease (>10 cm) for whom 3 cycles of CHOP may be inadequate treatment. In a subgroup analysis, no survival difference was found between the two groups when comparing patients presenting with non-bulky disease. Furthermore, in both the above studies, there was a high loco-regional failure rate after radiotherapy (21%).

The benefit of combined modality treatment has been reported in the rituximab era. The SWOG 0014 study reported a 4-year PFS of 88% and OS of 92% when rituximab was added to 3 cycles of CHOP plus IFRT (Persky *et al*, 2008). This represented an improvement over historical data from the pre-rituximab era (4-year PFS and OS of 78% and 88% respectively). The Mab-Thera International trial (MInT) trial, reported benefit in both OS and EFS when rituximab was added to CHOP-like chemotherapy in young (<60 years) patients with low risk IPI disease (Pfreundschuh *et al*, 2006). Most patients in this study had limited stage disease and IFRT was given to bulky (>7·5 cm) and extranodal disease. The optimal number of R-CHOP cycles for early stage disease is not clear. The German FLYER trial (NCT00278421) is currently comparing 4 vs. 6 cycles of R-CHOP for low IPI DLBCL patients.

Whilst there are no published randomized trials of radiation therapy (RT) in the rituximab era to guide treatment decisions, a single centre retrospective analysis demonstrated an improvement in OS and PFS for patients receiving RT in complete remission (CR) after 6–8 cycles of R-CHOP chemotherapy. For patients with Stage I and II disease, the 5-year OS and PFS with RT were 92% and 82% whereas without RT they were 73% and 68% respectively (Phan *et al*, 2010). Recently, by international consensus, the radiation volume has been further reduced from IFRT to a new concept of Involved Site Radiation Treatment (ISRT) (Illidge *et al*, 2014).

In conclusion, RT decreases local recurrence rates. For elderly patients and some younger patients with limited stage disease, 3–4 cycles of R-CHOP followed by ISRT may be

preferable, especially for sites where RT is well tolerated, e.g. groin, axilla and neck. In contrast, a full course of 6–8 cycles of R-CHOP may be preferable where RT might result in debilitating late toxicity, such as xerostomia following parotid treatment or increased breast cancer risk following mediastinal radiotherapy in younger women, albeit with the acknowledgement that the increased number of cycles of R-CHOP increases the risk of heart failure (Mulrooney *et al*, 2009).

Recommendations

- **It is recommended that patients with non-bulky (<7·5 cm) stage IA DLBCL presenting at sites associated with low morbidity for radiotherapy (e.g. groin, neck or axilla), be treated with 3–4 cycles of R-CHOP chemotherapy followed by ISRT of 30 Gy (1B). Six cycles of R-CHOP is an alternative and should be the preferred option if disease involves a site where the acute and late complications of RT are better avoided (1A).**
- **Patients with non-bulky stage IIA DLBCL should be treated with 6 cycles of R-CHOP (1A).**
- **Patients with bulky stage IA/IIA DLBCL should be treated with 6 cycles of R-CHOP followed by ISRT of 30 Gy to initial sites of bulk (1B).**

Advanced stage disease

Patients with stage III or IV DLBCL or those with any stage in the presence of B symptoms are treated as advanced stage disease. Several studies have shown the benefit of adding rituximab to CHOP, including the French GELA LNH 98-5 (Coiffier *et al*, 2002, 2010) and ECOG/CALGB 9703 (Habermann *et al*, 2006). The German RICOVER-60 study (Pfreundschuh *et al*, 2008b) demonstrated improvements in outcome following the addition of rituximab in elderly patients; the MInT study showed the same for younger patients with low IPI disease (Pfreundschuh *et al*, 2006).

The issue of dose density in the rituximab era was addressed by comparing R-CHOP-14 with R-CHOP-21 by the UK National Cancer Research Institute (NCRI) (Cunningham *et al*, 2013) and the French GELA LNH03-6B (Delarue *et al*, 2013) groups. Both studies showed no OS or PFS difference between R-CHOP-14 and R-CHOP-21. R-CHOP-21 therefore remains the standard treatment for advanced stage DLBCL.

The French GELA LNH03-2B compared intensified chemotherapy using 4 cycles of R-ACVBP followed by consolidation with 8 courses of R-CHOP chemotherapy in young (<60 years) patients with low IPI disease (Recher *et al*, 2011). Whilst survival was better in the R-ACVBP arm, results for the R-CHOP arm in this study were worse than would be expected for this good risk group of patients. As expected, the R-ACVBP regimen was also associated with greater toxicity. Dose-adjusted EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) with rituximab (DA-EPOCH-R) has also been reported to have significant activity, especially in GCB-type DLBCL, in a Cancer and Leukemia Group B (CALGB) multicentre phase II study (Wilson *et al*, 2008, 2012).

Patients with high-risk IPI DLBCL continue to have suboptimal outcomes in the rituximab era with predicted 5-year survival of 50–55% with R-CHOP. A number of studies have attempted to improve outcomes for high-risk patients using either dose intensifying regimens or autologous stem cell transplant (ASCT) in first remission. Four randomized trials comparing R-chemotherapy with upfront HDT and ASCT for high IPI disease were recently presented. Two trials showed a PFS benefit for HDT and ASCT but no impact, at present, on OS (US and Canadian intergroup SWOG S9704 trial; Italian Lymphoma Foundation DLCL04 trial)(Vitolo *et al*, 2012; Stiff *et al*, 2013), whilst two trials failed to demonstrate any benefit for HDT and ASCT (German DSHNHL 2002-1 trial; GOELAMS 075 trial)(Dilhuydy *et al*, 2010; Schmitz *et al*, 2012). Upfront HDT and ASCT therefore remain investigational approaches and cannot be recommended outside a clinical trial. Interestingly, the German DSHNHL 2002-1 trial showed a 3-year event-free survival (EFS) of 69·5% with R-CHOP plus etoposde (RCHOEP-14). Although not a randomized comparison with R-CHOP, this result in a large phase 3 randomized study represents a significant improvement over R-CHOP results in patients with high IPI disease. Early results from a prospective phase II NCRI UK study using the dose intense R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate/rituximab, etoposide, ifosfamide, cytarabine) regimen have also shown similarly encouraging results in this setting (McMillan *et al*, 2013a).

Patients with DHLs have poor outcomes with R-CHOP chemotherapy. Intensified chemotherapy regimens, such as R-CODOX-M/R-IVAC or DA-EPOCH-R, are sometimes used for treating Burkitt-like or grey zone lymphomas intermediate between DLBCL and Burkitt lymphoma. Transplant consolidation in first remission is also considered. At present there is insufficient evidence to recommend any of these strategies although retrospective studies suggest efficacy (Petrich *et al*, 2014).

Patients with DLBCL at risk of CNS disease should be considered for CNS prophylaxis. This is covered in a separate BCSH guideline (McMillan *et al*, 2013b).

IFRT consolidation has traditionally been used in trial protocols for bulky and extranodal disease. An exploratory analysis of the prognostic significance of maximum tumour (bulk) diameter (MTD) in young patients with good-prognosis DLBCL was performed in the MInT study. The multivariate analysis showed MTD to be an adverse prognostic factor after R-CHOP-like treatment, with 3-year OS of 98·0% for MTD <5·0 cm vs. 85·2% for MTD ≥10·0 cm (Pfreundschuh *et al*, 2006). This study prompted the

UNFOLDER study (NCT00278408) where patients with disease >7·5 cm were randomized to 36 Gy IFRT or no further treatment. The study was prematurely closed by the Independent Data Monitoring Committee in 2012 due to a highly significant advantage in PFS in patients receiving RT. In an amendment to the German RICOVER-60 trial, the value of adding 36 Gy IFRT to initial sites of bulk (>7·5 cm) or extranodal disease was evaluated. Patients receiving IFRT had superior EFS, PFS and OS (Held *et al*, 2014). A large prospective randomized trial comparing 30 Gy with 40–45 Gy showed no difference between the two arms (Lowry *et al*, 2011) Therefore, 30 Gy remains the recommended dose for consolidation therapy in patients with responsive disease using ISRT (Illidge *et al*, 2014). Whether radiotherapy can be avoided in patients achieving a PET-defined complete metabolic response to chemotherapy remains unknown and forms the basis of ongoing investigation. Patients with chemotherapy refractory disease require higher doses of radiotherapy (45–55 Gy), depending on the individual situation.

Response assessment

A negative PET scan at the end of treatment has a high negative predictive value (NPV) with a predicted 2-year PFS of 90–100%. However, the positive predictive value (PPV) is lower, reported as 50–82% (Spaepen *et al*, 2001; Micallef *et al*, 2011; Pregno *et al*, 2012). Biopsy of a PET-positive lesion is therefore advised prior to intensive salvage chemotherapy or, alternatively, an interval scan after 3 months if clinical suspicion of residual disease is low. The 5-Point Scale (Deauville criteria) is recommended for response assessment (Barrington *et al*, 2014; Cheson *et al*, 2014).

An interim PET scan during R-CHOP chemotherapy is less predictive of outcome (Yang *et al*, 2011; Yoo *et al*, 2011; Zinzani *et al*, 2011; Safar *et al*, 2012) than the end of treatment scan, with some studies reporting no difference in outcomes according to interim PET (Cashen *et al*, 2011; Micallef *et al*, 2011; Pregno *et al*, 2012). Therefore, treatment should not be altered solely on the basis of interim PET unless there is clear evidence of progression. PET findings should always be interpreted in relation to the clinical context and expected prognosis.

Recommendations

- **It is recommended that patients with advanced stage disease be treated with 6–8 cycles of R-CHOP-21. Variants of this regimen include 6 cycles of R-CHOP-21 or R-CHOP-14, each followed by 2 additional rituximab doses (1A).**
- **There is no established standard of care for patients with poor risk IPI disease. R-CHOP is often used but RCHOEP-14 and RCODOX-M/R-IVAC are alternatives (2C).**
- **CNS prophylaxis is recommended for selected patients as per published BCSH guidelines (McMillan *et al*, 2013b) (2B).**
- **HDT and ASCT are not recommended in first remission outside a clinical trial (1C)**
- **There is no accepted standard of care for patients with double hit lymphoma. Treatment options include R-CHOP with CNS prophylaxis, R-CHOEP-14, DA-EPOCH-R or R-CODOX-M/R-IVAC. These patients may be considered for a transplant consolidation in first remission (2C).**
- **Where feasible, it is recommended that patients receive ISRT to initial sites of bulk (>7·5 cm) and extranodal disease after completing immunochemotherapy (1B).**
- **Outside of a clinical trial, identifying ABC/GCB subtypes of DLBCL should not influence treatment decisions (1C).**
- **The PPV of an interim PET scan is variable with insufficient evidence at present to change standard treatment based on the result of interim PET-CT scan alone. A routine interim PET scan is therefore not recommended (1C).**
- **An end of treatment PET scan is strongly recommended (1A).**
- **The PPV of a PET-positive lesion is variable; biopsy is therefore advisable prior to second line treatment. Alternatively, consider an interval scan after 3 months if clinical suspicion of residual disease is low (1B). ISRT to the PET-positive lesion may be an option in selected cases where biopsy is not possible or desirable (2C).**

Relapsed/refractory disease in the transplant-eligible patient

Confirmatory biopsy and restaging are strongly recommended. Factors predicting prognosis at relapse include the secondary age-adjusted IPI (sAAIPI) (Hamlin *et al*, 2003; Lerner *et al*, 2007) and relapse within 1 year of R-CHOP (Gisselbrecht *et al*, 2010). For those deemed fit for intensive therapy, HDT followed by ASCT is recommended. The main goal of salvage is to reduce disease burden and demonstrate continued chemotherapy sensitivity prior to ASCT. Although CR is not necessarily required, pre-transplant PET scan is highly predictive of outcome following ASCT (Spaepen *et al*, 2003; Derenzini *et al*, 2008; Hoppe *et al*, 2009), with best outcomes reported in those achieving a complete metabolic remission (Johnston *et al*, 2008; Sauter *et al*, 2015). The majority of favoured first-line salvage regimens include either one or both of a platinum agent or ifosfamide, and there is no clearly superior regimen (Gisselbrecht *et al*, 2010). Choice should therefore be based upon consideration of side-effect profiles, cost and lack of potential detrimental impact on the ability to collect stem cells. Whilst addition of rituximab to salvage regimens improves response rates in rituximab-naïve

patients (Kewalramani *et al*, 2004; Vellenga *et al*, 2008), similar data are lacking for those with prior exposure. Nevertheless, salvage with a regimen incorporating an anti-CD20 monoclonal antibody is generally recommended.

For patients who do not respond to first-line salvage, outcomes are extremely poor with 1–3 year survival rates of <10% (Ardeshna *et al*, 2005; Elstrom *et al*, 2010). Although many clinicians attempt a second-line salvage regimen, the ultimate curability of these patients is limited, and they should be considered for clinical trials of novel agents.

In the pre-rituximab era, survival benefit was demonstrated for patients consolidated with ASCT after achieving a CR with salvage chemotherapy (Philip *et al*, 1995). Other studies have reported that about a third of patients achieving a partial remission (PR) also experience long-term disease-free survival with ASCT, which is better than historical results with chemotherapy alone (Kewalramani *et al*, 2000; Vose *et al*, 2001; Rodriguez *et al*, 2004). Although response rates to salvage are lower in the rituximab era, outcomes following ASCT appear similar in chemotherapy-sensitive patients (Smith *et al*, 2011; Moore *et al*, 2012; Mounier *et al*, 2012), and recommendations regarding ASCT are therefore the same.

The most commonly used conditioning regimen for ASCT is BCNU, etoposide, cytarabine and melphalan (BEAM), although other chemotherapy-based regimens appear to yield broadly comparable outcomes (Stockerl-Goldstein *et al*, 1996). Chemotherapy-only regimens are generally preferred due to the long-term toxicity of total body irradiation (TBI)-based regimens (Armitage, 2003), with the possible addition of localized radiation to sites of persistent disease (Biswas *et al*, 2010). Incorporation of radioimmunotherapy in conditioning remains investigational and routine use cannot be recommended (Vose *et al*, 2013). No benefit has been shown from using post-transplant rituximab maintenance (Gisselbrecht *et al*, 2012). Finally, there is insufficient evidence for tandem ASCT (Haioun *et al*, 2001).

The role of radiotherapy consolidation before or after ASCT is unclear, with some studies showing benefit particularly for those with large volume residual lesions (Hoppe *et al*, 2009; Biswas *et al*, 2010), whilst others report no impact (Friedberg *et al*, 2001; Wendland *et al*, 2007). Targeting therapy to patients with lesions showing persistent PET activity following salvage might be a rational approach in the absence of further data. The dose must be individualized, but higher doses of up to 55 Gy may be required for cases presenting with loco-regional problems or chemotherapy-refractory disease. No clear recommendations can be made on the merits of pre- *versus* post-ASCT RT.

The prognosis of patients relapsing after ASCT is very poor (Vose *et al*, 1993). Nevertheless a minority will respond to salvage chemotherapy and may be considered for allogeneic stem cell transplant (alloSCT) (Rezvani *et al*, 2008; Thomson *et al*, 2009; Sirvent *et al*, 2010; van Kampen *et al*, 2011; Bacher *et al*, 2012; Freytes *et al*, 2012). Time to relapse following ASCT, and sensitivity to salvage chemotherapy are the most important prognostic factors. AlloSCT is therefore not recommended in those achieving less than a PR.

Defining a group of patients who should be considered for alloSCT in preference to ASCT is challenging. Currently there is no evidence that any specific high risk sub-groups benefit from alloSCT *versus* ASCT. Overall survival outcomes are similar for alloSCT and ASCT, with higher non-relapse mortality (NRM) following alloSCT counterbalancing higher relapse with ASCT (Aksentijevich *et al*, 2006; Lazarus *et al*, 2010). Although neither option can therefore be recommended over the other, alloSCT using a conventional donor is a reasonable clinical option for younger patients (age <40–50 years) with high risk features, or in those in whom ASCT is not possible due to inadequate stem cell dose.

The choice between myeloablative and reduced intensity conditioning strategies for alloSCT is similarly challenging, as comparative studies are flawed by differing selection criteria (Rodriguez *et al*, 2006; Bacher *et al*, 2012; Hamadani *et al*, 2013). In general, myeloablative alloSCT may be considered in patients <40 years of age who have not had a prior ASCT with a reduced intensity alloSCT being preferred for all others.

Recommendations

- **Repeat biopsy is strongly recommended to confirm relapse (1A).**
- **Transplant-eligible patients should receive intensive salvage chemotherapy with a non-cross resistant regimen followed by ASCT consolidation in those achieving CR (1A).**
- **In those achieving a PR, second line salvage chemotherapy can be given followed by ASCT if CR is achieved, or consolidation by ASCT in PR can be considered (2B)**
- **Response assessment by PET scan prior to ASCT is desirable (2B).**
- **Peri-transplant radiotherapy to sites of disease presenting particular loco-regional problems should be considered, particularly if residual PET-positive lesions are detected following salvage (2B).**
- **There is no clearly defined group where alloSCT is preferable to ASCT, but it may be an option for some younger patients with high-risk disease, especially if stem cell dose is inadequate for ASCT (2C).**
- **Selected patients relapsing post-ASCT may be considered for further salvage and alloSCT (2B).**

HIV-associated DLBCL

Development of HIV-associated DLBCL is related to older age, lack of prior treatment with combined antiretroviral therapy (cART) and low CD4 cell count (Engels *et al*, 2010). Patients typically present with advanced stage disease and

extranodal involvement, but survival is now approaching that seen in HIV-negative patients (Coutinho *et al*, 2014). Treatment is usually with either R-CHOP or infusional regimens, such as R-EPOCH, with no randomized data to favour one over the other. A recent multicentre retrospective UK study reported excellent outcomes with R-CHOP (Coutinho *et al*, 2014). Although a previous phase III randomized study reported increased rate of infectious complications with the addition of rituximab to CHOP in patients with a CD4 count of $<0{\cdot}05 \times 10^9$/l of blood (Kaplan *et al*, 2005), subsequent phase 2 studies and a recent meta-analysis have confirmed the benefit of adding rituximab (Ribera *et al*, 2008; Barta *et al*, 2012). Thus addition of rituximab to chemotherapy is recommended for all patients with appropriate antimicrobial (co-trimoxazole, fluconazole and aciclovir) and granulocyte colony-stimulating factor (G-CSF) prophylaxis. Although there is some debate, in Europe it is common to continue cART during chemotherapy, avoiding boosted protease inhibitors where possible (William *et al*, 2014). For a detailed discussion of HIV-associated lymphomas please refer to the British HIV Association guidelines (Bower *et al*, 2014).

Patients with relapsed disease should be treated similarly to HIV-negative patients. Those with chemotherapy-sensitive disease achieve similar outcomes with ASCT consolidation to those of HIV-negative patients (Balsalobre *et al*, 2009; Diez-Martin *et al*, 2009; Krishnan *et al*, 2010).

Recommendations

- **Patients with HIV-associated DLBCL should be treated with R-CHOP with concomitant cART (1A). R-EPOCH is a suitable alternative (2B).**
- **All patients should receive antimicrobial (co-trimoxazole, fluconazole and aciclovir) and granulocyte colony-stimulating factor prophylaxis (1A).**
- **Patients with relapsed disease should be treated similarly to HIV-negative patients, including using ASCT for chemotherapy-sensitive relapse (1B).**

Management of the elderly, frail or unfit patient with DLBCL

The side effect profile of R-CHOP worsens with increasing comorbidity, functional disability (van de Schans *et al*, 2012; Boslooper *et al*, 2014; Merli *et al*, 2014; Wieringa *et al*, 2014) and advancing age (Kobayashi *et al*, 2011; Lin *et al*, 2012). Consequently, in practice only a minority of patients >80 years are treated with full dose R-CHOP. Their outcome, especially following the attainment of CR, is comparable to that of patients aged less than 80 years (Varga *et al*, 2014) making it imperative to undertake a careful assessment of fitness for R-CHOP before considering less toxic and potentially less effective alternatives. There is no uniformly accepted age cut-off to define an 'elderly' patient as it is applied variably to those aged >60, >65 or >70 years in different studies, with patients >80 years being classified as 'very elderly'. Tools such as the comprehensive geriatric assessment (CGA) (Olivieri *et al*, 2012; Spina *et al*, 2012) or the simpler Charlson comorbidity index (Kobayashi, *et al* 2011, Lin *et al*, 2012) may assist physician judgment in identifying those patients who are suitable for R-CHOP. Using this approach, two prospective studies of CGA-modified R-CHOP in patients aged over 70 years reported 5-year OS of 46% for all patients (Olivieri *et al*, 2012) and 76%, 53%, 29% for fit, unfit and frail patients respectively (Spina *et al*, 2012). Treatment-related mortality in both studies was relatively low at 14–17%.

As demonstrated by the DSHNHL group, steroid pretreatment of patients with a WHO performance status of >2 may render them suitable for standard R-CHOP (Pfreundschuh *et al*, 2004; Pfreundschuh, 2010). Primary G-CSF prophylaxis in patients >65 years with poor performance/nutritional status or significant comorbidity reduces the risk of febrile neutropenia and related morbidity with R-CHOP and, in line with European Organisation for Research and Treatment of Cancer guidelines, routine use is recommended to improve treatment tolerance (Repetto *et al*, 2003).

Modified regimens have been evaluated in patients unsuitable for full-dose R-CHOP. The French GELA group reported 2-year OS and PFS of 59% and 47% respectively using R-mini-CHOP in patients aged >80 years, predominantly with advanced stage disease and without significant comorbidity or lymphoma-related organ impairment (Peyrade *et al*, 2011). The treatment-related mortality was 21%. Two other retrospective studies corroborate the use of dose reduced R-CHOP in patients aged 60 to >80 years (Shin *et al*, 2012; Aoki *et al*, 2013). Co-morbidity may necessitate replacement of vincristine (peripheral neuropathy), prednisolone (diabetes mellitus) or doxorubicin (cardiac disease or risk factors) (Spina *et al*, 2012) by an alternative drug. Phase ll data support consideration of R-GCVP (rituximab, gemcitabine, vincristine, prednisolone) (Fields *et al*, 2014) or R-COMP14 (Biweekly rituximab, cyclophosphamide, vincristine, non-pegylated liposome-encapsulated doxorubicin, prednisone) (Corazzelli *et al*, 2011) in patients unfit for doxorubicin.

Recommendations

- **There is no uniformly accepted age cut-off to define an 'elderly' patient. Treatment decisions should be based on assessment of fitness/frailty and co-morbidities rather than age alone (1A).**
- **Patients considered fit for intense treatment should be treated with standard R-CHOP as this produces best outcomes (1B).**
- **Modified R-CHOP with dosage and/or individual drug adjustments should be considered for those unfit for standard treatment (2C).**

- **Patients with impaired performance status (WHO > 2) at presentation, should be considered for a steroid pre-phase prior to assessing fitness for standard or modified R-CHOP (2B).**
- **Primary G-CSF prophylaxis is recommended for patients aged >65 years, frail patients and those with significant comorbidities (1A).**

Follow-up

Patients who achieve a CR following treatment should be followed up on a 3–4 monthly basis for up to 2 years. Outside a clinical trial, there is no role for routine surveillance scans during post-treatment follow-up and patients should be assessed clinically. The risk of relapse beyond 2 years is <10% (Larouche *et al*, 2010; Vose *et al*, 2010). It is therefore reasonable to discharge patients back to their primary care physician at that stage with advice and support.

Conflict of interests

The BCSH paid the expenses incurred during the writing of this guidance. None of the authors had conflicts of interest to declare.

All authors have made a declaration of interests to the BCSH and Task Force Chairs which may be viewed on request.

Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website(www.bcshguidelines.com). If minor changes are required due to changes in level of evidence or significant additional evidence supporting current recommendations a new version of the current guidance will be issued on the BCSH website.

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