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Diagnosis and treatment of diffuse large B-cell lymphoma

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Summary

Diffuse large B-cell lymphoma (DLBCL) is the most frequently-occurring type of malignant lymphoma in the Western world. It has an aggressive natural history, with a median survival of less than one year if left untreated. Immunochemotherapy regimens, consisting of the anti-CD20 antibody rituximab typically in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), are currently the treatment backbone. Despite remarkable progress in improving patient survival, clinical outcomes are still unsatisfactory for certain subsets of patients, including the elderly and very elderly and those with highly aggressive disease. This review outlines some of the current treatment strategies for DLBCL and discusses the main issues that affect clinical practice.

Key words: *DLBCL; first-line treatment; maintenance treatment; relapsed/refractory disease; rituximab; chemotherapy; staging; follow-up*

Abbreviations

aaIPI = age-adjusted International Prognostic Index; ABC = activated B-cell – like; ACVBP = doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone; ASCO = American Society of Clinical Oncology; BCCA = British Columbia Cancer Agency; CALGB = Cancer and Leukaemia Group B; CEPP = cyclophosphamide, etoposide, procarbazine and prednisone; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CNS = central nervous system; CORAL = Collaborative Trial in Relapsed Aggressive Lymphoma; CR = complete response; CT = computerised tomography; DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; DSHNHL = German High-Grade Non-Hodgkin's Lymphoma Study Group; EFS = event-free survival; EORTC = European Organization for Research and Treatment of Cancer; ESHAP = etoposide, solumedrol, high-dose cytarabine and platinum; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ESMO = European Society for Medical Oncology; FIL = Italian Lymphoma Foundation; FISH = fluorescence in-situ hybridisation; GCB = germinal centre B-cell – like; G-CSF = granulocyte colony-stimulating factor; GELA = Groupe d'Etude des Lymphomes de l'Adulte; HDT = high dose therapy; HIV = human immunodeficiency virus; ICE = ifosfamide, carboplatin and etoposide; IFRT = involved-field radiation therapy; IPI = International Prognostic Index; LDH = lactate dehydrogenase; MInT = MabThera International Trial; NCCN = National Comprehensive Cancer Network; NHL = Non-Hodgkin's lymphoma; NOS = not otherwise specified; OS = overall survival; PET = positron emission tomography; PMBL = primary mediastinal B-cell lymphoma; PFS = progression-free survival; R = rituximab; RICOVER-60 = Rituximab with CHOP over age 60 years; SCT = stem cell transplantation; SAKK = Schweizerische Arbeitsgruppe für Klinische Krebsforschung; SWOG = Southwest Oncology Group; WHO = World Health Organisation.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently-occurring lymphoma, accounting for an estimated 35% of all lymphoma cases worldwide. In the Western world, nearly 90% of aggressive mature B-cell lymphomas are identified as DLBCL. This heterogeneous disease has a complex classification, and if left untreated, takes an aggressive and fatal clinical course. Patients typically present with nodal or extranodal disease, usually exhibiting rapid

tumour growth and symptoms that are highly dependent upon the tumour localisation.

For over 25 years, the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen was the gold standard for the treatment of DLBCL. Today, the addition of monoclonal antibodies such as rituximab (R) has altered the therapeutic landscape and improved clinical outcomes. However, despite recent advances in the classification and molecular profiling of the disease, its biological heterogeneity still hampers diagnosis, prognosis and treatment. Compounding this challenge, more than half of the patients diagnosed with DLBCL are over 60 years of age. Thus, today's clinician has to walk the line between efficacy and tolerability for a disease in which many issues remain to be resolved with respect to aetiology, pathology and treatment.

The present review aims to discuss some of the key issues that affect clinical practice with respect to the diagnosis, treatment, and follow-up of DLBCL patients.

Diagnosis and staging

B-cell lymphomas are malignant cellular proliferations that arise at various steps during the process of normal B-cell development occurring in the primary lymphoid organs and secondary lymphoid tissues or at various non-lymphoid sites [1]. DLBCL is a large B lymphoid cell neoplasm with a diffuse growth pattern composed of large B-lymphocytes with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of normal lymphocytes (fig. 1). Morphological, biological and clinical studies have identified distinct morphological variants, molecular and phenotypic subgroups and clinico-pathological entities amongst DLBCL [2]. Yet, most DLBCL cases would be finally classified as DLBCL not otherwise specified (NOS), not meeting the classification criteria of a specific subtype as proposed by the current World Health Organisation (WHO) system of classification [2].

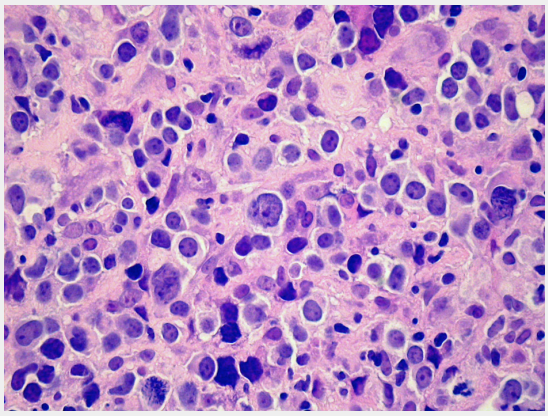

Figure 1

Typical morphological appearance of DLBCL.

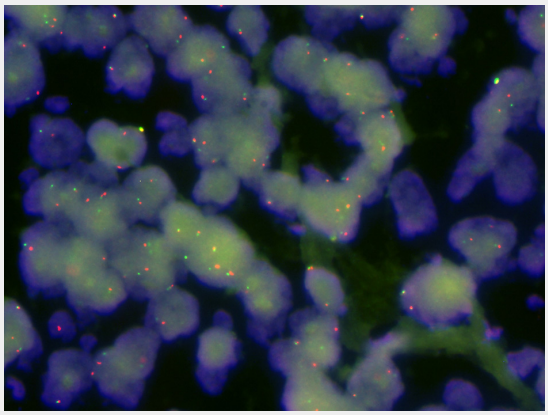

Figure 2

C-MYC gene rearrangement, demonstrated by a "break-apart" FISH probe. Note free green and red signals corresponding to the rearranged allele as well as fused signals corresponding to the second non-rearranged allele.

The WHO divides DLBCL into subtypes based on clinical, morphological, immunological and genetic features (table 1) [3, 4]. There are three main morphologic variants each with its own characteristic cytological parameters: centroblastic, immunoblastic and anaplastic, with the immunoblastic variant being associated with the worst prognosis [5]. Unfortunately, the identification of immunoblastic variants is often not reproducible [2]. Phenotypically, over 95% of DLBCL cases express pan-B-cell markers, such as CD20 [6]; a few phenotypic markers such as FoxP1 and Cyclin E are consistently associated with poor outcome [7]. The prognostic value of Bcl-2 expression has been abolished by the incorporation of rituximab into standard therapeutic regimens [8].

DLBCL probably arises via a stepwise process of somatic mutations, particularly chromosomal translocations involving oncogenes and, often, promoter regions of the immunoglobulin genes. The genes most commonly rearranged in DLBCL are *BCL6* (over 30% of cases), *BCL2* (approximately 20% of cases) and *C-MYC* (5–10% of cases). Somatic point mutations in other genes including *CARD11*, *A20* and *TNFRSF11A* leading to NF-κB pathway activation are also observed in 10 to 20% of cases [9]. Except for rearrangements of *C-MYC*, all other recurrent genetic abnormalities in DLBCL have not yet been linked to a specific outcome. DLBCL with *C-MYC* rearrangements (fig. 2) has a poorer prognosis and is poorly responsive even to rituximab plus CHOP (R-CHOP) therapy, with approximately 50% of patients showing early relapses or progressive disease [10–12].

Gene expression profiling divides DLBCL into three molecular subtypes, germinal centre B-cell – like (GCB) DLBCL, activated B-cell – like (ABC) DLBCL and primary mediastinal B-cell lymphoma (PMBL). The GCB-like cases are associated with better prognosis and respond well to etoposide and rituximab [13], whereas ABC-like cases have a poorer prognosis but could benefit from the addition of bortezomib [14] and rituximab [15] to a CHOP-like regimen. Nevertheless, gene expression data do not capture all the biological parameters that influence diagnosis and response to therapy. Attempts at phenotypic stratification of DLBCL have failed to reliably classify the disease into GCB and ABC subtypes [16], leaving gene-profiling as the current gold standard.

The clinical variables with prognostic significance in DLBCL such as age, disease stage, serum lactate dehydrogenase (LDH) levels, performance status and extranodal

involvement form the basis of the International Prognostic Index (IPI) (table 2). The IPI has prognostic value independent of molecular subtyping. Due to the importance of age in determining treatment and outcome, the age-adjusted IPI (aaIPI; table 2) is widely used in the management of elderly DLBCL patients, and includes only three of these prognostic factors (performance status, disease stage and LDH level) [17].

Currently, the only reliable diagnosis of DLBCL is obtained through tissue-based histopathological examination. Whenever possible, excisional biopsies are preferred over core needle biopsies in order to ensure sufficient tissue for morphological and molecular analysis [18]. The current ESMO guidelines also highlight the importance of obtaining enough material [19]. Once diagnosis has been established, the patient undergoes staging, which involves medical history, physical examination and blood chemistry testing including LDH and uric acid. Screening for HIV, Hepatitis B and C as well as protein electrophoresis are also recommended. In case of positivity for hepatitis B surface antigen (HBsAg) or antibodies to hepatitis B core antigen (anti-HBc), prophylactic treatment with an antiviral drug needs to be considered during and several months after treatment with immunochemotherapy regimens containing a B-cell-specific antibody, because of potentially fatal hepatitis reactivation [20].

Imaging techniques routinely used for staging prior to therapy include contrast-enhanced computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scanning. ESMO guidelines suggest at least a CT scan of the chest and abdomen in patients eligible for curative therapy [19, 21], while giving a strong recommendation for the use of PET scanning to better delineate the extent of the disease [22].

The role of ^{18}FDG-PET in DLBCL

The use of interim PET/CT scanning is currently the focus of many clinical trials in DLBCL. The prognostic and predictive value of this procedure may be assessed at various timepoints: at initial diagnosis, after two to four treatment cycles (interim PET/CT), at the end of treatment, in the follow up phase, at the time of relapse, after the induction of salvage treatment and after salvage high-dose therapy. PET/CTs are performed not only to improve diagnostic accuracy but are increasingly used to guide treatment decisions. Along with Hodgkin's lymphoma, DLBCL belongs to the group of the intensely ^{18}FDG-PET "avid" tumours [23]. Although the procedure results in upstaging of about 10–20% of the cases at initial diagnosis, this fact rarely alters the choice of treatment. Consequently, an initial PET/CT may not be absolutely necessary. However, the use of PET/CT scanning for initial staging of DLBCL is strongly recommended in current clinical guidelines [24]. In addition, since interim or later PET/CTs may become more important, nuclear medicine specialists place emphasis on the fact that images taken at initial diagnosis are mandatory or at least helpful to reliably assess PET images taken during or at the end of treatment.

The role of interim PET/CT scanning to monitor response during therapy is currently one of the most debated questions in clinical trials and has led to conflicting results [25–31]. This question was also addressed in a trial run by the Schweizerische Arbeitsgruppe für Klinische Krebsforschung (SAKK; trial 38/07). Interim results of this trial have been recently published [32]. Although a negative interim PET is strongly associated with a durable complete response, a positive PET after only two or four cycles of R-CHOP14 cannot reliably predict outcome [32]. At present, the use of interim (mid-treatment) PET/CT scanning for response assessment in DLBCL is only recommended within clinical trials [24, 33, 34].

In current daily practice, PET/CT scanning has its clearest role in restaging patients at the end of treatment. In this setting, PET/CT scanning has a high negative predictive value (between 85% to over 90%) in patients with Hodgkin's lymphoma or DLBCL. Data from the Vancouver lymphoma group have suggested that in patients with residual abnormalities ≥2 cm on conventional CT scan, PET/CT may help to select individuals who need consolidative radiation after the end of chemotherapy [35]. Studies are also underway to evaluate PET/CT scanning after the induction of salvage treatment to decide whether the use of autologous or allogeneic stem cell transplantation is more appropriate.

In conclusion, PET/CT scanning in DLBCL has been shown to be most useful at the time of initial staging and at the end of primary treatment, whereas the value of interim PET scanning to monitor response and guide treatment decisions is much less clear. In the setting of relapsed disease, PET/CT scanning may be helpful in guiding treatment approaches; however, more data are needed in order to generate reliable treatment algorithms.

First-line treatment

If left untreated, DLBCL has a median survival of less than 1 year [36]. Prior to the rituximab era, anthracycline-based chemotherapy regimens alongside involved-field radiation formed the basis of treatment [37, 38]. The introduction of the chimaeric monoclonal anti-CD20 antibody rituximab a decade ago was a milestone in the treatment of B-cell lymphomas including DLBCL, greatly improving progression-free survival (PFS) and overall survival (OS) [39–41].

Elderly patients (60-80 years)

In general, patients over 60 years are classified as elderly; this population comprises over half of those diagnosed with aggressive disease [42]. The original data illustrating the benefits of R-CHOP therapy was established in elderly patients. Based on the results of earlier Phase II trials in patients with indolent and aggressive lymphomas, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) conducted a study comparing eight cycles of R-CHOP against eight cycles of CHOP alone administered every 21 days in patients over 60 years of age. R-CHOP21 resulted in significantly higher complete response rates (76% vs. 63% for CHOP alone; P = 0.0005) and two-year OS rates (70% vs. 57% for CHOP alone; P = 0.007) [43]. These findings have been confirmed in the five- and ten-year follow-up results, which showed statistically-significant benefits in favour of R-CHOP in terms of PFS, OS, event-free survival (EFS) and disease-free survival (DFS); (P = 0.00001, P

= 0.0073, P = 0.00002, P = 0.00031, respectively) [44, 45]. The GELA findings were corroborated independently in the E4494 study run by the US Intergroup [46].

The results from the RICOVER-60 trial have added new information on the R-CHOP dosing schedule [47]. The trial was based on a bifactorial design comparing six versus eight cycles of CHOP14 with or without eight cycles of rituximab in patients between 60–80 years of age. All patients received recombinant granulocyte colony-stimulating factor (G-CSF) support. The findings reported by Pfreundschuh et al. suggest that a dose-dense treatment schedule may improve outcomes, particularly in patients with poor prognosis. Six cycles of R-CHOP14 followed by two cycles of rituximab (6xR-CHOP14 + 2R) significantly improved EFS, PFS and OS compared to six cycles of CHOP14; extending chemotherapy to eight cycles conferred no additional clinical benefits. An important aspect of the RICOVER-60 trial was the high compliance to the dosing regimen (≥98% and ≥95% median relative dose for the six- and eight-cycle regimens, respectively). The introduction of pre-phase treatment (1 mg vincristine once and 100 mg prednisone daily around 1 week prior to the first CHOP cycle) has greatly minimised the first-cycle effect and tumour lysis syndrome, allowing for the successful completion of therapy in most patients [47, 48].

Although the RICOVER-60 trial was based on a dose-dense R-CHOP regimen, the superiority of R-CHOP14 versus the standard R-CHOP21 regimen still lacks formal clinical validation. Surprisingly, data from a trial by the UK NCRI do not indicate the superiority of dose-dense R-CHOP [49, 50]. Results from this trial showed no differences in either complete or overall response rates, or failure-free and overall survival. Of note, this trial was not restricted to patients between 60–80 years of age; around half of the patient cohort were younger patients between 18–60 years of age. Similarly, the recently presented second interim analysis of the LNH03-6B trial did not support the hypothesis of the higher efficacy of dose dense R-CHOP14 over R-CHOP21 with respect to EFS, PFS and OS [51]. Long-term follow up is needed before establishing a preferred dosing regimen. For the time being, both R-CHOP14 and R-CHOP21 will remain in the front line as standard-of-care therapies for patients above 60 years of age.

Table 1: DLBCL variants, subgroups and subtypes (from Jaffe et al. [116]).

DLBCL, not otherwise specified
Common morphologic variants:
Centroblastic
Immunoblastic
Anaplastic
Rare morphologic variants
Molecular subgroups
GCB
ABC
Primary mediastinal large cell lymphoma
Immunohistochemical subgroups
CD5-positive DLBCL
GCB-like
non-GCB – like
DLBCL subtypes
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
EBV-positive DLBCL of the elderly
Other lymphomas of large B-cells
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
ALK-positive LBCL
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Primary effusion lymphoma

Table 2: The International Prognostic Index (IPI) [117] and age-adjusted IPI [118] for Non-Hodgkin's Lymphoma.

Risk Factor	**0 Point**	**1 Point**
IPI		
Age	≤60 years	>60 years
Ann Arbor stage	I or II	III or IV
Serum LDH level	Normal	Above normal
Number of extranodal sites of involvement	≤1	>1
ECOG performance status	0–1	≥2
aaIPI (≤60 years or >60 years)		
Ann Arbor stage	I or II	III or IV
Serum LDH level	Normal	Above normal
ECOG performance status	≤1	>1

Several lines of evidence suggest that there is potential for improving clinical outcomes by further exploiting rituximab dosing. First, pharmacokinetic data from the RICOVER-60 trial showed that rituximab trough serum levels increased slowly and only reached a plateau after the fifth or sixth administration. The DENSE-R-CHOP14 trial explored the effect of four additional rituximab applications during the first 3 weeks to the standard regimen of eight rituximab and six CHOP14 cycles (for a total of 12 applications of rituximab). Preliminary data from this study suggest higher immediate rituximab serum levels and higher complete response rates [52]. However, these results have not been fully published yet and will need to be confirmed by independent data. Gender appears to matter in the treatment of DLBCL patients with male patients having lower rituximab trough serum levels and poorer three-year PFS (relative risk for progression 1.6; P = 0.004) compared to female patients. This question is being investigated in the ongoing DENSE-R-UP-CHOP14 study in which female patients receive 375 mg/m^2 and male patients receive 500 mg/m^2 [53].

Very elderly patients (>80 years)

The majority of clinical trials on elderly DLBCL patients have excluded patients over 80 years of age. Due to the lack of data, treatment of this group of very old patients is controversial [54]. In a retrospective analysis of patients over 80 years of age, Italiano et al. showed that the addition of rituximab to reduced-dose CHOP chemotherapy provides a good compromise between toxicity and efficacy [55]. Results from one of the first prospective studies in patients over 80 years of age combining rituximab with a dose-reduced CHOP regimen (R-miniCHOP) showed promising clinical response and two-year OS rates of 59% [56]. The only factor influencing OS was a serum albumin concentration of ≤35 g/L (hazard ratio 3.2, 95% CI 1.4–7.1; P = 0.0053). The good tolerability profile allowed the majority of patients to complete the planned treatment and supports the application of a dose-reduced chemotherapy regimen in the very elderly. The potential for achieving disease cure is still a valid option for this patient subgroup, encouraging clinicians to consider an R-CHOP – based regimen in elderly patients with good performance status. For elderly patients not eligible to receive R-CHOP therapy, exploratory studies on alternate chemotherapy partners (such as bendamustine) for rituximab have also showed promising results, though these need to be confirmed in larger numbers of patients [57].

Young patients (18–60 years)

The treatment of younger patients with DLBCL is generally stratified according to disease risk assessed by aaIPI score. In patients with no more than one risk factor according to the aaIPI, six to eight cycles of R-CHOP21 is currently the mainstay of most treatment regimens [19, 58]. In practice, many oncologists have begun using R-CHOP14 – based treatment regimens, analogous to that used in the RICOVER-60 trial. There is no evidence that the therapeutic index of this regimen is inferior to that of R-CHOP21, and furthermore the use of R-CHOP14 offers the patient a substantially shorter time on treatment (three vs. five months).

Young, low-risk patients

The MInT trial was one of the first studies to demonstrate the benefits of rituximab plus CHOP chemotherapy over chemotherapy alone. In this study, a total of 824 patients aged 18–60 years with 0–1 risk factors according to the aaIPI were randomised to six cycles of CHOP or CHOP-like chemotherapy, either with or without rituximab followed by radiotherapy to bulky and extranodal sites [59]. A key finding was that the incorporation of rituximab conferred significant survival benefits with respect to EFS as well as OS compared to chemotherapy alone in younger good-prognosis patients with newly diagnosed DLBCL. In a recent update, the improvement in PFS (79.9% vs. 63.8%; P <0.0001) and OS (89.8% vs. 80%; P = 0.001) for immunochemotherapy was maintained after a median follow-up of 70 months [60]. Multivariate analysis demonstrated that EFS, PFS and OS were affected not only by the addition of rituximab, but also by aaIPI score and the presence of bulky disease. Consequently, two subgroups amongst younger patients with good prognosis could be distinguished: those with a very favourable prognosis (aaIPI = 0 with no bulky disease) and a less favourable subgroup (aaIPI = 1 and/or bulky disease) [60]. Based on these results, the ongoing FLYER study (DSHNHL-2004-2) run by the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) will test the feasibility of a dose reduction (by comparing four versus six cycles of CHOP-21 chemotherapy with six applications of rituximab in each treatment arm) in the subgroup of young patients with very favourable prognosis with the aim of reducing toxicity without compromising efficacy. Results from this trial will be complemented by the UNFOLDER study (DSHNHL-2004-3) investigating whether dose-dense application of the R-CHOP regimen every two weeks has improved efficacy compared to the standard R-CHOP-21 regimen in the less favourable prognosis subgroup.

The LNH03-2B study conducted by the GELA explored the combination of eight cycles of rituximab with an intensive ACVBP (doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone) regimen against a standard arm with eight cycles of R-CHOP21 in younger DLBCL patients with an aaIPI of 1. The rationale for this study was based on previously published findings demonstrating the superiority of ACVBP over CHOP21 alone in patients with DLBCL in the pre-rituximab era [61, 62]. Compared to patients in the R-CHOP21 arm, patients treated with R-ACVBP had significantly improved three-year EFS (80.9% vs. 66.7%, p = 0.0035), PFS (86.8% vs. 73.4%, p = 0.0015) and OS (92.2% vs. 83.8%, p = 0.0071) [63]. However, the ACVBP regimen was associated with more treatment-related toxicities, particularly Grade 3–4 haematological events. Long-term follow-up results from this study are needed before the risk-benefits of R-ACVBP versus R-CHOP can be properly assessed. Although no direct comparison between the results of this trial and the previously mentioned MInT trial can be made, it is nonetheless interesting to note that the outcome of the corresponding subgroup of patients with 1 risk factor in the MInT trial treated

with only six cycles of R-CHOP21 appears to be similar to the more intensively-treated subgroup in the R-ACVBP arm and even superior to the standard arm with eight cycles of R-CHOP in the GELA study. The fact that only patients in the MInT trial received radiotherapy for bulky or extranodal disease – whereas no radiotherapy was planned in the GELA trial – raises the question on the value of radiotherapy after the full course of immunochemotherapy in DLBCL patients. The eagerly awaited UNFOLDER trial will address the role of consolidative radiotherapy in this setting.

Young, high-risk patients

Although it has not been formally validated, the combination of rituximab plus CHOP is accepted as the benchmark against which new dosing regimens or agents are measured [64, 65]. There is currently no consensus on the optimal treatment for younger patients with unfavourable aaIPI scores (aaIPI 2-3) and the best option for these patients is to enrol them in well-designed clinical trials. Intensified variants to the CHOP regimen have been tested, including the addition of etoposide (CHOEP21: 100 mg/m^2 on days 1–3), and the use of recombinant human G-CSF alongside dose-dense CHOP14 or CHOEP14 [66]. Notably, the addition of rituximab to CHOEP or CHOP equalised the benefit of etoposide in a young, good-prognosis patient population [59]. However, in a recent population-based investigation from the Danish Lymphoma Group, the R-CHOEP14 regimen compared favourably with the R-CHOP14 regimen (without etoposide) in young high-risk patients with 2–3 risk factors according to the aaIPI (4-year OS 75% vs. 62%, p = 0.04, respectively) [67]. To assess the clinical outcome and influence of various biomarkers in a group of patients treated with dose-adjusted R-EPOCH, the CALGB is investigating germinal centre B-cell (GCB) and post-GCB subtypes by immunohistochemistry [13]. The combination of R-CHOP with bortezomib is being tested in those with the ABC subtype [14]. Dose-adjusted R-EPOCH was shown to overcome the negative prognostic value of translocated *C-MYC* [68]. Other dose-intensive regimens are being explored, including R-ACVBP [69, 70].

One of the most extensively debated issues in this context is the role of up-front high dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) for younger patients with high risk disease. A meta-analysis of 15 randomised controlled trials failed to demonstrate a clear benefit for HDT with ASCT as first-line therapy [71]. Recently, the results of four additional randomised trials incorporating rituximab have been presented. In the GOELAMS075 trial, eight cycles of R-CHOP14 resulted in a similar three-year PFS/DFS compared to rituximab plus HDT (76% vs. 83% respectively, for both treatment arms) but R-CHOP14 was better tolerated [72]. Similarly, HDT with R-MegaCHOEP14 followed by ASCT was no more effective than eight cycles of R-CHOEP14 but was associated with a much higher incidence of infections in the DSHNHL Phase III trial in young high-risk DLBCL patients with 2–3 risk factors according to the aaIPI [73]. The two-year PFS results were similar in both arms, with even superior results for the R-CHOEP14 regimen in the subgroup of patients with only 2 risk factors according to the aaIPI. Overall, the R-CHOEP14 regimen resulted in an excellent PFS (73.7%) and OS (84.6%) in this poor-prognosis population. On the basis of these encouraging results, the DSHNHL is currently investigating whether optimized rituximab administration can further improve the outcomes of the R-CHOEP14 regimen. In contrast, HDT followed by ASCT after four cycles of R-CHOP14 or R-MegaCHOP14 (R-HDC + ASCT) resulted in a superior two-year PFS compared to the pooled population of standard R-CHOP14 or R-MegaCHOP14 in the DLCL04 trial conducted by the FIL [74]. So far, this advantage in PFS has not been translated into an OS benefit and longer follow-up will be needed to clarify the role of HDT in this setting. It is noteworthy that the two-year PFS curves in both the non-ASCT arms were superimposable, showing similar results for eight cycles of R-CHOP14 and six cycles of the investigational dose-intensified R-MegaCHOP14 regimen. Finally, the results of a U.S./Canadian Intergroup trial (SWOG S9704) have recently been presented [75]. After induction therapy with five cycles of CHOP21 (± rituximab), 253 of 397 enrolled patients were randomly assigned to either three additional cycles of CHOP (± rituximab) or one additional cycle of CHOP (± rituximab) followed by HDT with ASCT. Two-year PFS was 69 and 56%, respectively [hazard ratio: 1.72; 95% CI: 1.18-2.51; p = 0.005] in favour of HDT over conventional therapy. However, there was no difference in OS between the treatment arms (71% versus 74%, respectively, p = 0.32). Exploratory analysis indicated that the majority of clinical benefits occurred in the high risk group (aaIPI = 3). Nevertheless, these conclusions should be interpreted with caution as only 44 patients in each treatment arm belonged to the latter group.

Taken together, these clinical data do not unequivocally demonstrate the superiority of consolidation therapy with HDT and ASCT as first-line therapy over six to eight cycles of CHO(E)P-like chemotherapy combined with eight doses of rituximab. In accordance with the current ESMO guidelines, these new regimens remain experimental. It is highly recommended that young patients with poor prognosis are treated within a clinical trial [19].

Abbreviated therapies

In patients with “limited disease” (usually defined as stage I and non-bulky stage II disease), the use of abbreviated chemotherapy followed by involved-field radiation therapy (IFRT) has been the subject of clinical trials [76]. The advantages of this abbreviated regimen are thought to be 1) decreased risk of cardiotoxic effects due to the lower total dose of doxorubicin, 2) the use of two treatments without cross-resistance, and 3) the direct application of radiotherapy to sites of disease [77]. The SWOG initially demonstrated that three cycles of CHOP followed by IFRT was superior to eight cycles of CHOP in patients with localized DLBCL in terms of five-year PFS and OS (77% vs. 64%, P = 0.03; and 82% vs. 72%, P = 0.02, respectively) [77]. However, the initial superiority of the combined approach disappeared with longer follow-up [78], indicating that the shorter duration of therapy may be associated with higher relapse rates [58]. A later study conducted by the SWOG showed that the addition of four cycles of rituxim-

ab to abbreviated CHOP in combination with IFRT resulted in even higher PFS and OS rates than CHOP alone (PFS: 93% at 2 years and 88% at 4 years; OS: 95% at 2 years and 92% at 4 years) [79]. However, in this trial a continuing pattern of relapse without a plateau in either the PFS or OS curves was noted, suggesting that the abbreviated immunochemotherapy regimen may have failed to eradicate the malignant clone. Another hypothesis raised is that limited-stage DLBCL may be a separate molecular entity from advanced-stage disease, warranting further investigation into specific treatment regimens for this subgroup of patients [79, 80].

Recently, Sehn et al. presented data from 134 patients with non-bulky, limited stage I and II disease using a PET-based approach to tailor therapy: patients with a negative PET scan (n = 103) following three cycles of R-CHOP received only one additional cycle of R-CHOP, whereas PET-positive patients received IFRT. After a median follow-up of 30 months, seven of 103 patients have relapsed and the three-year OS was 96%. However, in the group of patients with a positive PET scan after three cycles of R-CHOP, treatment with IFRT was unsatisfactory with high (9/30 patients) distant relapse rates [81]. The results from this publication suggest that in those with localized disease, PET scanning might aid in identifying patients who may benefit from abbreviated chemotherapy. However, the appropriate treatment for patients with a positive PET scan after immunochemotherapy remains to be validated.

The role of radiotherapy

There is much controversy over the benefits of radiotherapy in the treatment of DLBCL. Radiotherapy has generally been used in combination with chemotherapy either with or without rituximab for the treatment of patients with localised disease. Two randomised studies showed that consolidation RT can improve EFS and OS in patients with stage I/II disease. The SWOG study (discussed above) was one of the first to show the potential benefits of three cycles of CHOP followed by IFRT in patients with stage I or non-bulky stage II disease [77]. These results have been supported independently in a retrospective analysis by the British Columbia Cancer Agency (BCCA) [82]. In contrast, a GELA trial (93-4) in elderly patients (>60 years) did not establish any benefits for the addition of IFRT to four cycles of CHOP [83]. In a separate study conducted by the GELA, ACVBP alone was shown to be superior to IFRT plus CHOP in a group of younger patients with localised disease [62], though this regimen has not been widely implemented due to increased toxicity [84].

The conflict surrounding the use of radiotherapy is partly a result of key unanswered questions on the biology of DLBCL. What are the clinical definitions for “limited stage”, “early-stage” or “localised” disease? There is currently great heterogeneity amongst the patient populations included in these clinical trials. Patients within the stage I-II categories have dramatically different survival outcomes: those with stage I or IE disease respond well regardless of therapeutic regimen, whereas those with bulky (any mass >10 cm) Stage II disease resemble those with advanced disease in terms of prognosis and treatment outcomes [84].

The results of the MInT trial for young, good prognosis patients offer some insight into the role of radiotherapy in the treatment of this subgroup. The study cohort as defined by stage, IPI risk factors and bulky disease included patients with bulky stage I or stage II–IV disease (with 0–1 aaIPI risk factors). Radiotherapy at doses of 30–40 Gray was given to patients with bulky disease (defined as more than 5 cm in diameter). Retrospective subgroup analysis showed that the most favourable subset (those with no risk factors or bulky disease) had a 90% survival without radiotherapy. Bulky disease emerged as a strong independent prognostic factor for EFS, PFS and OS, even though patients with bulky disease received additional radiotherapy [59, 85]. A historical comparison of two DSHNHL studies conducted in elderly patients showed no benefits of additional radiotherapy in patients with bulky disease who had already achieved complete response after six cycles of R-CHOP14. However, radiotherapy may be beneficial in elderly patients with bulky disease achieving only a partial remission after completion of immunochemotherapy [86]. As discussed in the previous section, the superiority of the MInT trial results (where patients with bulky disease received radiotherapy) against those of the LNH03-2B trial (no radiotherapy used) continues to fuel the radiotherapy debate. The UNFOLDER study will provide further insight into the role of consolidative radiotherapy for bulky and/or extranodal disease.

Additional efforts are underway exploring the use of PET scanning to focus radiation therapy on PET-positive residual masses. Recently, Sehn et al. reported on a series of 196 patients with advanced-stage disease who had residual abnormalities >2 cm on end-of-treatment CT scans after 6–8 cycles of R-CHOP immunochemotherapy. All patients underwent additional PET scanning. Patients with a negative PET scan were observed (regardless of initial or residual bulk), while patients with a positive PET scan received consolidative radiation therapy to the PET-positive sites: this resulted in an outcome similar to those with a negative PET upon completion of R-CHOP therapy [35]. This observation suggests a role for PET-guided consolidative radiotherapy for patients with residual masses on end-of-treatment imaging following immunochemotherapy.

Treatment of relapsed disease

Despite the improved efficacy of first-line treatment regimens, a significant proportion of patients experience disease progression or relapse. The outlook for this subgroup is dismal, with a median survival time of 6 months or less [87, 88]. The standard approach to relapsing DLBCL is high-dose therapy and autologous stem cell transplantation (SCT). Prior to the rituximab era, results from the PARMA trial demonstrated improved event-free survival (EFS) and OS in chemosensitive patients who received a platinum and cytarabine-based chemotherapy regimen (DHAP) in combination with autologous SCT, compared to those who received DHAP treatment alone [89, 90]. Since then, additional salvage regimens have been explored either alone or with the use of rituximab, including ESHAP [91, 92] EPOCH [93], CEPP [94, 95] and ICE [96, 97].

The clinical impact of relapsing disease has been re-evaluated in the rituximab era. The high efficacy of R-CHOP as a first-line therapy has led to a smaller proportion of relapses, but those who relapse present a significant clinical challenge. The choice of salvage therapy in patients who failed first-line therapy was explored in the Phase III CORAL trial [98]. A total of 396 relapsing DLBCL patients were randomised to receive three courses of either R-ICE or R-DHAP salvage therapy; responders were given HDT and autologous SCT. No significant differences were seen between R-ICE and R-DHAP in terms of overall response rates, three-year PFS and OS. Multivariate analysis revealed three main factors that influenced OS: second-line aaIPI ≥2, relapse occurring <12 months after first-line treatment, and prior rituximab exposure. Interestingly, the retrospective evaluation of the prognostic value of the cell of origin using the Hans algorithm revealed that patients with GCB-like DLBCL had an improved outcome with regards to PFS and OS when treated with R-DHAP compared with R-ICE. The independent prognostic impact of the cell of origin interaction with treatment was confirmed in multivariate analysis. These results demonstrate that the cell of origin is an important predictive factor for the response to non-anthracycline-based immunochemotherapy salvage regimens in patients with relapsed/ refractory DLBCL [99].

The poor results of standard high dose therapy (HDT) plus autologous SCT – particularly for rituximab-pretreated patients with only about 20% achieving long-term second remissions [98] – underscore the need for new treatment strategies for patients who relapse after front-line and salvage rituximab-containing therapy. A plethora of new therapeutic agents targeting the various pathways linked to the pathogenesis of DLBCL are currently under investigation [100]. However, detailed discussion of these is beyond the scope of this review.

Allogeneic SCT is being explored as an alternative in the subset of patients who relapse after first-line therapy and who do not respond to salvage regimens. In general, this treatment is reserved only for patients with poor prognosis, refractory disease, or who have failed autologous SCT [101]. Although some studies have shown lower relapse rates and better survival outcomes for allogeneic compared to autologous SCT, the high treatment-related mortality underlies the reluctance of clinicians to recommend this for all but a small subset of patients [102]. Recently, the use of reduced-intensity conditioning regimens has shown promising results [103, 104], but the optimal dosing schedules remain to be defined. A French study in 68 patients who had failed two therapeutic regimens prior to undergoing reduced-intensity conditioning followed by allogeneic SCT yielded two-year OS, PFS and relapse rates of 49%, 44% and 41%, respectively [105]. Interestingly, multivariate analysis revealed that prior anti-CD20 therapy did not affect the incidence of disease progression or relapse following the transplant. Allogeneic SCT is associated with a graft-versus-lymphoma effect that could reduce the chances of post-transplantation relapse [88], but the final outcome is heavily dependent upon tumour histology [106]. Thus, the question of optimal patient selection based on disease characteristics is a major barrier to establishing the efficacy of allogeneic SCT and the appropriate conditioning regimens.

Relapsing patients who are not eligible for transplant pose a significant clinical challenge, as few treatment options are available. Currently, several alternative salvage regimens are being explored. The use of six to eight cycles of rituximab in combination with gemcitabine-based regimens has shown encouraging results [107, 108]. However, the same patterns emerge, with non-responders faring poorly (OS for relapsed elderly patients <1 year). Similar to the situation in post-transplant survival, the degree of chemosensitivity is the primary factor dictating clinical outcomes following salvage therapy. In the rituximab era, patients experiencing relapse likely harbour disease with a distinct molecular signature requiring novel therapeutic agents. Patients falling into this category are recommended to receive treatment within a clinical trial.

CNS prophylaxis

Secondary involvement of the central nervous system (CNS) in DLBCL is an infrequent event with usually fatal consequences. The incidence is between 4–8% [109–111]. Evaluation of the cerebrospinal fluid by flow cytometry combined with conventional cytology greatly increases the rate of detection of clinically occult leptomeningeal disease, compared to assessment by conventional cytology only [112]. A work-up with examination of the cerebrospinal fluid is usually recommended in patients with paranasal sinus, testicular, epidural, or bone marrow involvement or if more than two extranodal sites are involved.

With no effective therapies available for CNS relapse, many experts advocate the use of prophylactic therapy for high-risk patients. Authorities including ESMO, BCCA, and the National Cancer Comprehensive Network (NCCN) recommend the routine use of CNS prophylaxis in high-risk populations [19], but there is no clear consensus on the type of therapy. The analysis of the RICOVER-60 patient cohort suggested that intrathecal methotrexate played no part in preventing CNS disease in patients who had been treated with immunochemotherapy, except in patients with testicular lymphoma [113]. More recently, the role of systemic chemotherapeutic drugs able to cross the blood-brain barrier (in particular high- or intermediate-dose methotrexate) has been emphasized supported by some data from clinical trials [114, 115]. Some studies have shown CNS relapse rates of 2–3% in patients receiving intrathecal or high-dose methotrexate, compared to 5–8% in those who received only immunochemotherapy without CNS prophylaxis [116]. On the basis of the current data, there is a rationale favouring the use of systemic high-dose methotrexate over intrathecal methotrexate for CNS prophylaxis in high-risk patients [117]. However, the optimal prophylactic regimen as well as more accurate predictors of CNS relapse need to be identified before any progress can be made with respect to the prevention of secondary CNS disease.

The widespread use of rituximab in front-line treatment regimens may affect the incidence of CNS relapse. Analysis of CNS events in the RICOVER-60 patient cohort suggested that the incorporation of rituximab to CHOP reduced

the risk of CNS involvement [113], a finding that has been supported by some groups [118] and challenged by others [119]. Recent data suggests that the protective effect is most apparent in patients achieving a complete remission with R-CHOP immunochemotherapy indicating that the beneficial effect of rituximab may be through improved control and eradication of systemic disease [118]. Some of the reasons for the conflicting views stem from the heterogeneity in the different study populations, variations in front-line and prophylactic regimens, and a lack of agreement as to which subgroup of patients should receive CNS prophylaxis [109, 110, 120]. Consistently emerging risk factors for CNS relapse include high IPI score, involvement of more than one extranodal site, poor performance status, elevated LDH levels, and involvement of testes, orbit or paranasal sinuses [113, 118, 120].

Supportive care and follow-up

During therapy, prophylaxis and treatment of systemic infections are key to improving patient outcomes. Chemotherapy-induced myelosuppression leading to severe neutropenia greatly increases the risk of infectious complications and might compromise the dose intensity of the curative treatment [121]. The intensity of the chemotherapy regimen, presence of advanced disease, co-morbidities and age are amongst the risk factors associated with the likelihood of developing febrile neutropenia. The American Society for Clinical Oncology (ASCO) and the European Organisation for Research and Treatment of Cancer (EORTC) have included the use of G-CSF in their guidelines for the supportive treatment of high-risk patients [122, 123]. As febrile neutropenic events are more likely to occur during the early cycles of chemotherapy, G-CSF should be given early in the course of treatment [124]. The DSHNHL recommends the use of acyclovir and cotrimoxazole [21, 47].

At the end of therapy, a complete restaging is performed. According to ESMO guidelines and a recent review, PET scanning is highly recommended for post-treatment assessment [24]. Bone marrow aspirate and biopsy should only be repeated at the end of treatment if initially involved.

There are no formally established guidelines on the specific procedures recommended for response evaluation and follow-up. In general, patient follow-up procedures are similar after first-line as well as after relapse treatment. ESMO guidelines recommend the patient to undergo medical history and physical examinations every three months for the first year after therapy, then every 6 months for the following two years and once a year thereafter [19]. Although repeat CT scanning at 6, 12 and 24 months after end of treatment is common practice, there is no definitive evidence that routine imaging for patients in complete remission provides any outcome advantage [19, 121]. As the majority of relapses occur during the first two years following therapy, careful clinical assessment during this time window is critical in order to catch any signs of disease progression.

Conclusions

The outlook for patients with DLBCL has improved, with survival rates nearly doubling over the past ten years. The introduction of rituximab to established chemotherapy regimens such as CHOP and ACVBP was a major breakthrough, allowing many patients to achieve disease cure. The clinician, however, must continue to navigate through the maze of new dosing regimens while balancing the patient's clinical status alongside unresolved issues in lymphoma biology. There is room for improvement, particularly in the treatment of the elderly and those with high-risk disease. Future improvements in clinical outcomes depend upon acquiring a greater understanding of the pathogenesis of DLBCL. Indeed, the differing sensitivities of patients with the same stage of lymphoma to a single treatment regimen underscore the fact that there are additional parameters governing response to treatment not captured by our current system of classification. New combinations of antibodies with improved biological activity or new drugs that act in concert with R-CHOP-like regimens may help to target highly malignant tumour cells that are characteristic of high-risk disease. Additional correlations between biological parameters, therapeutic response and clinical outcomes need to be incorporated into future clinical trials to pave the way for biology-driven DLBCL therapy.

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Figures (large format)

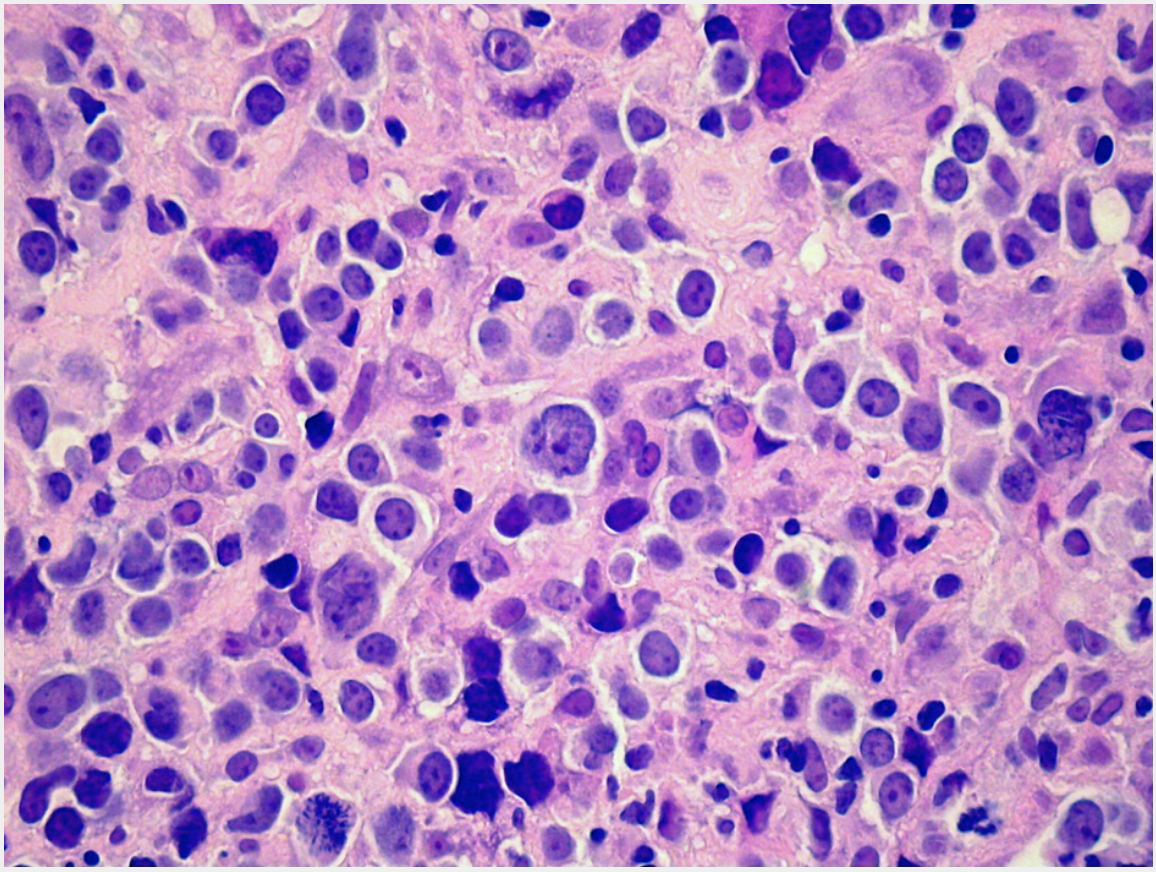

Figure 1

Typical morphological appearance of DLBCL.

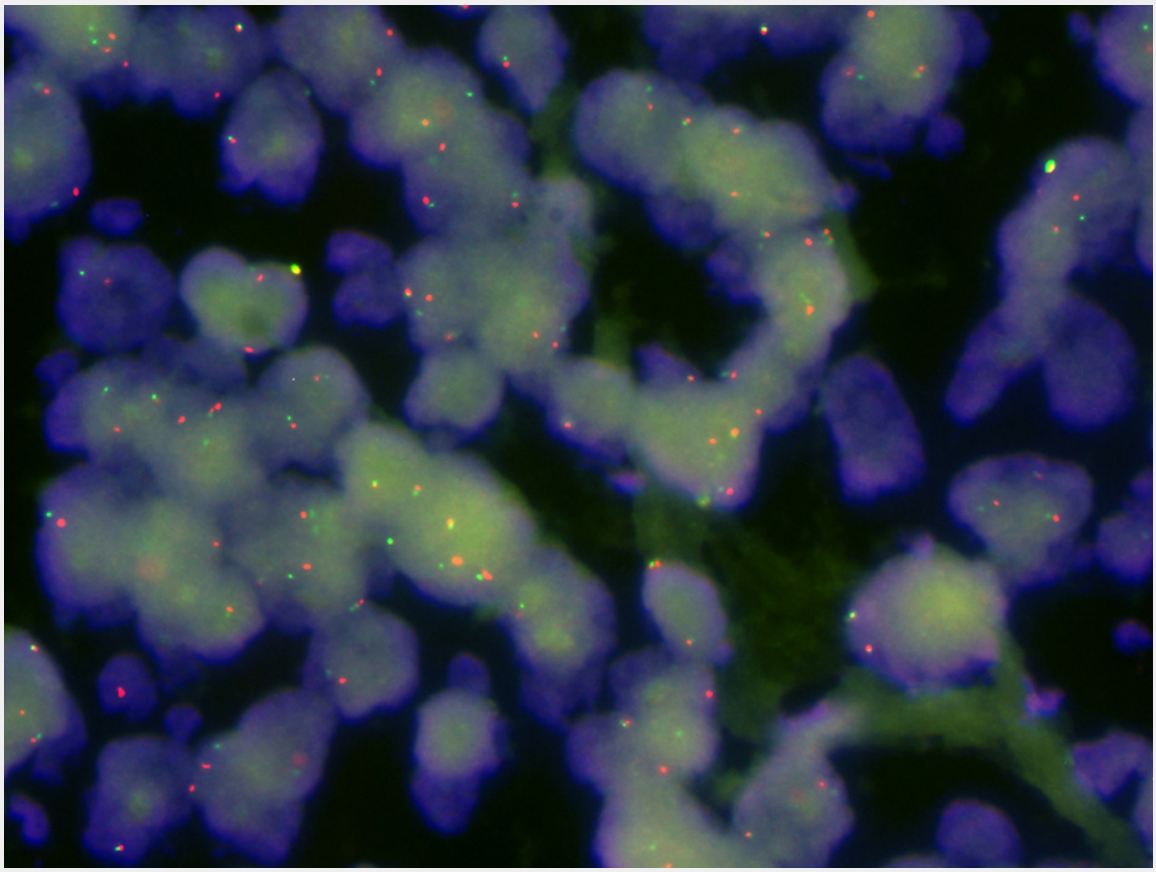

Figure 2

C-MYC gene rearrangement, demonstrated by a “break-apart” FISH probe. Note free green and red signals corresponding to the rearranged allele as well as fused signals corresponding to the second non-rearranged allele.