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Letter
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Double Hit Lymphoma Diagnosis and Treatment in Europe—A Cross-Sectional Survey of Clinical Practice by the EHA Lymphoma Working Party (EHA LyG)

Igor Aurer[1], Martin Dreyling[2], Massimo Federico[3], Herve Tilly[4], Kim Linton[5], Eva Kimby[6], Martine E. D. Chamuleau[7], Marie Jose Kersten[7]

Correspondence: Igor Aurer (e-mail: igor.aurer@mef.hr).

High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, colloquially known as "double hit lymphoma" (DHL) was only formally defined as a lymphoma subtype in the latest version of the WHO classification.[1] This entity encompasses tumors of diffuse large B-cell (DLBCL), blastoid and Burkitt lymphoma (BL) morphology plus chromosomal translocations of *MYC* and either *BCL2* or *BCL6* or both. The diagnosis therefore requires performance of fluorescent in situ hybridization (FISH) on tumor samples, an assay not routinely used in the diagnosis of DLBCL. Approximately 5% of morphologically and immunohistochemically (IHC) defined DLBCL cases are DHL. Many belong to the germinal center (GC) subtype and have increased protein expression of MYC and BCL2 and/or BCL6 (double expressors (DE)).[2–4] There is no consensus between pathologists on the criteria for defining DE (which is not considered a separate entity in the current WHO classification) by IHC cutoff levels and different studies yield conflicting results on the frequency of DHL in the non-GC subtype of DLBCL.[5–8]

DHL is considered to be a lymphoma subtype more aggressive than DLBCL-NOS. Recent reports suggest that only translocations with the IgH locus display a dismal prognosis but may represent only half of the high risk patients.[9] Most authors recommend using more intensive therapies, based on case series or single-arm studies on patient with aggressive lymphomas with *MYC* rearrangements despite the fact that no regimen is established to be superior to R-CHOP.[10–13]

The variable use of FISH may significantly influence the diagnostic yield and prognostic characteristics of DHL with DLBCL morphology. There are no European, e.g. ESMO, guidelines for treatment or prescreening and testing may be restricted in clinical practice, such as only performing FISH in DE patients or in GC subtype DLBCL patients. We surveyed lymphoma experts across Europe to identify recommendations and standard practices for using FISH in suspected cases of DLBCL. We also collected information on recommendations and standard practices regarding treatment of patients with DHL with DLBCL morphology.

Lymphoma experts from different European countries were representatives of groups and countries and/or members of the Special Working Group on Lymphomas of the European Hematology Association (EHA LyG). Experts from 26 countries were contacted during 2018–19 to complete a questionnaire about recommendations and common practices in diagnosis and treatment of suspected DHL and DLBCL, 23 responses relating to diagnosis and 22 related to treatment were received.

The number of inhabitants per country was extracted from the Eurostat database for European Union member states[14] and Wikipedia for non-member states.[15]

FISH recommendations

Ten countries lacked general recommendations on criteria for FISH testing. Of the remaining countries, four recommended testing for all DLBCL cases; three for DE irrespective of subtype, two for DLBCL of GC subtype irrespective of MYC, BCL2 and BCL6 expression, one for all GC cases and non-GC DE, and one for DE of the GC subtype. In two countries screening was

[1]Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb and Medical School, University of Zagreb, Zagreb, Croatia
[2]Department of Medicine III, Ludwig Maximillian University Hospital, Munich, Germany
[3]Medical Oncology, CHIMOMO Department, University of Modena and Reggio Emilia, Modena, Italy
[4]Dept of Hematology and U1245, Centre Henri Becquerel, Université de Rouen, France
[5]Division of Cancer Sciences, University of Manchester, Manchester Cancer Research Centre, Manchester, United Kingdom
[6]Unit of Hematology, Department of Medicine at Karolinska Institutet, Stockholm, Sweden,
[7]Department of Hematology, Amsterdam University Medical Center, Amsterdam, Netherlands
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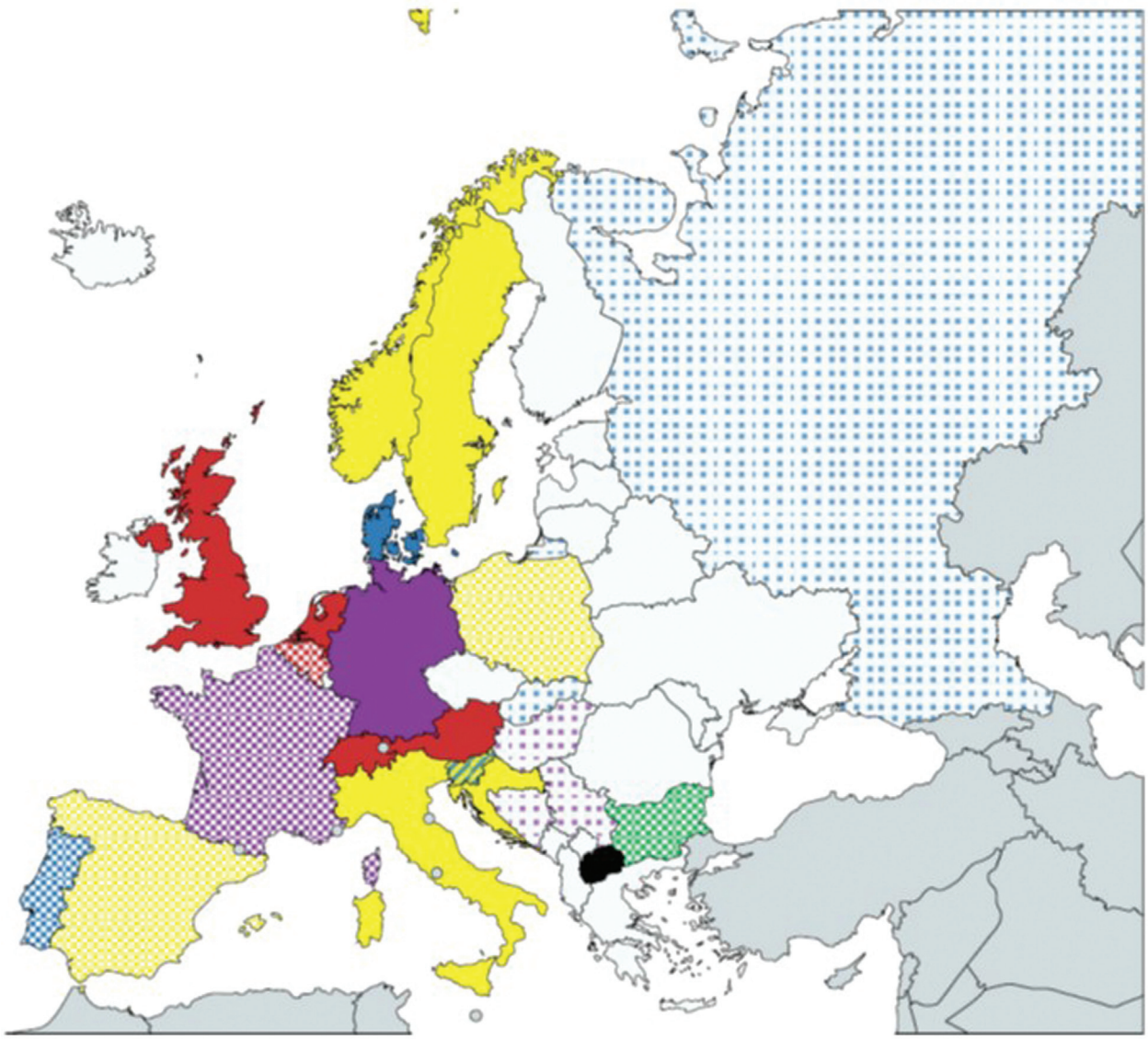

Figure 1. Performance of FISH for double hit lymphoma in patients with lymphoma with diffuse large B-cell (DLBCL) morphology. White: no information; Red: all DLBCLs; Blue: GC-type DLBCL; Yellow: double expressors irrespective of cell of origin; Green: double expressors of the GC-type; Purple: at the discretion of the pathologist and/or treating physician; Black: not performed at all. Stripes: GC-type DLBCL and double expressor; Checkers and dots: FISH performed in limited number of centers.

generally recommended only for patients with high-risk features, and in one for those with very high LDH irrespective of IHC features. The criteria for defining MYC positivity by IHC staining varied between 40% and 80% positive tumor cells, for BCL2 between 10% and 80% and for BCL6 between 10% and 60%. The Hans' algorithm was universally used for differentiating between GC and non-GC subtypes.

FISH availability

In 12 European countries with approximately 270 million inhabitants FISH was available to all patients requiring testing according to recommendations or the opinion of the hemato-pathologist or treating physician. The availability of FISH in other countries varied significantly; in 6 countries with approximately 180 million inhabitants FISH was not available to patients treated at some hospitals; in two additional countries with approximately 150 million inhabitants it was available only to patients with certain insurance types; and in two countries with approximately 9 million inhabitants availability was dependent on the limited resources of the diagnostic laboratory. FISH for DHL was not available at all in one country with approximately 2 million inhabitants (Fig. 1).

Treatment recommendations

Official general treatment recommendations did not exist in 11 countries, including 2 in which FISH was performed in all DLBCL cases. DA-R-EPOCH was recommended in all 11 countries with recommendations. In some countries alternative regimens were also recommended, including those used for treating BL in 5 and R-CHOEP14 in three. In one country, the use of "regimens more intensive than R-CHOP" was recommended.

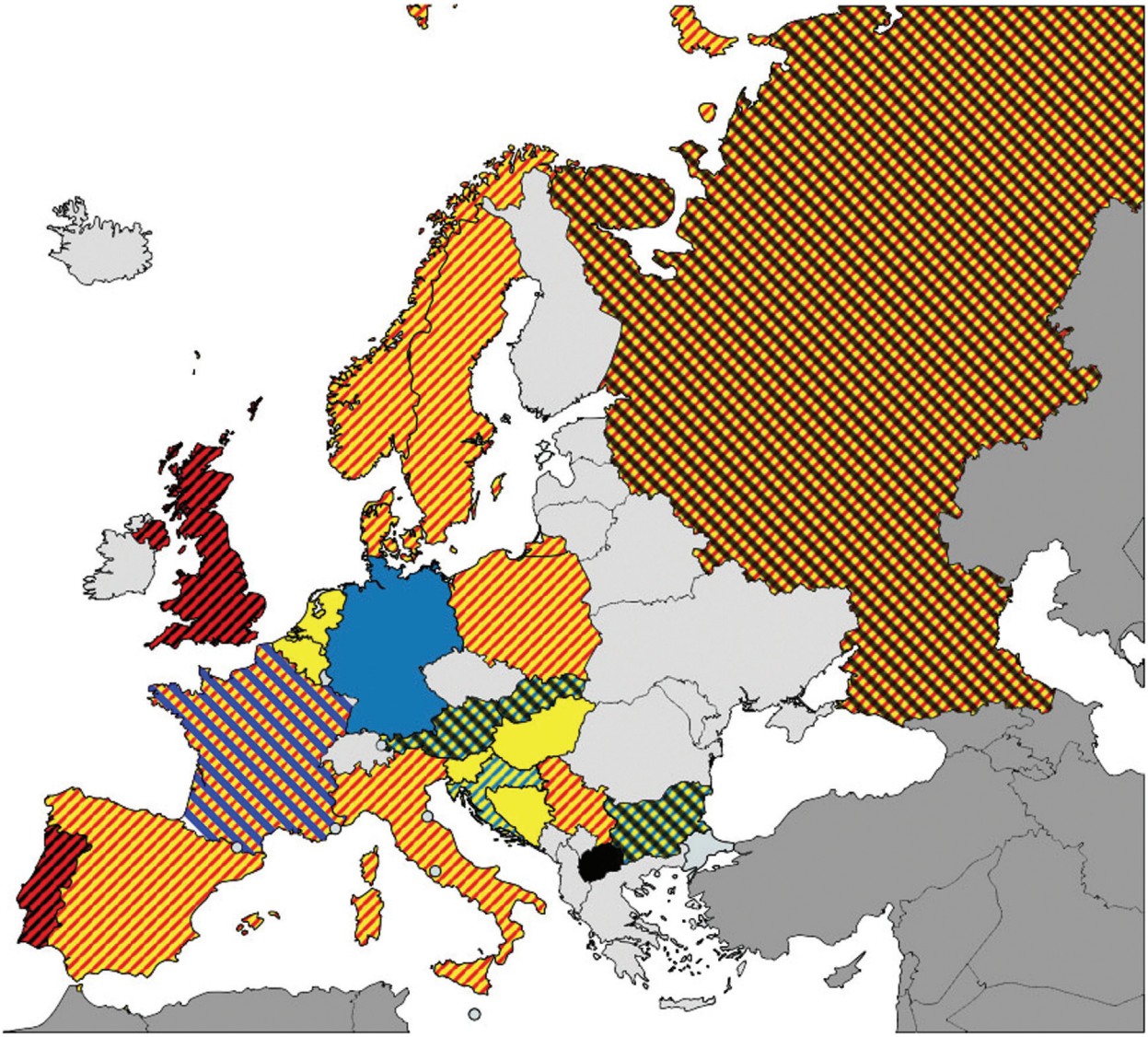

Figure 2. **Treatment of patients diagnosed with double hit lymphoma with DLBCL morphology White: no information; Yellow: DA-R-EPOCH; Red: Regimens used for treating Burkitt lymphoma; Blue: R-CHOEP14 or R-ACVBP; Black: R-CHOP. In countries with more than one color, more than one type of regimen is routinely used.**

Clinical practice

DA-R-EPOCH is used for treating DHL patients in 18 countries, BL regimens in eleven, R-CHOEP in 5 and R-ACVBP in one (the numbers add to more than 22 because more than one regimen is used in some countries). R-CHOP is used in some fit patients diagnosed with DHL who could tolerate more aggressive approaches in 4 countries, including two with recommendations for general diagnostic screening but not for treatment (Fig. 2).

Results of this survey revealed unexpected high variability in the criteria for FISH testing in suspected DHL and DLBCL. Fewer than half of responding countries have official recommendations for FISH testing in patients with DLBCL. In some, despite recommendations, testing is not available to patients treated at some hospitals. Most recommendations limit testing to patients with a higher expected frequency of positive findings, but there is no consensus on the optimal target population for testing. Availability of FISH is also determined to some extent by the country's wealth and organization of diagnostic services; countries with general availability are either those in which testing is recommended for all patients or those with centralized hematopathological diagnostics. There is also variation in the definition of DE between expert hematopathologists, sometimes even from a single country, indicating the need for development of consensus diagnostic criteria. These findings suggest that current practice is likely to miss a diagnosis of DHL in a proportion of patients, especially those with low-risk clinical features or treated outside of centers of excellence. This is mainly due to limitations in FISH availability. Under-diagnosis should be taken into account when describing the epidemiology, characteristics and prognosis of DHL patients.

Treatment recommendations are lacking in half of the responding countries. Despite this, treatment practice is less variable and most centers offer intensive therapy despite a relatively low level of supporting evidence. This may indicate

general recognition of this entity as a very aggressive lymphoma with a poor prognosis. DA-R-EPOCH is the most frequently used treatment, followed by BL regimens. Some patients, mostly outside of academic centers, remain undiagnosed due to limited FISH availability and therefore do not receive recommended treatment. A few countries offer R-CHOP even to patients deemed fit for more intensive approaches.

Discussion

Results of this survey were derived from responses of a small number of experts (1–4 per country) in lymphoma treatment or diagnostics collected from mid-2018 to mid-2019. Some inconsistencies or inaccuracies in the data were observed, possibly indicating non-uniformity of guidelines within some countries or responses reflecting personal rather than institutional/country policy. Recommendations and practices may also have changed since the data collection period. Despite these limitations, we believe that these data represent a realistic and valuable snapshot of practices in DHL diagnostics and treatment across Europe.

In conclusion, we found a high variability and different models for restricted FISH testing in suspected DHL patients across Europe. Treatment approaches are more uniform, applying intensified treatment in most DHL patients. These data underscore the need of either universal testing or guidelines for (restrictive) testing, as well as pan-European clinical trials in this rare lymphoma entity. Future projects of the EHA LyG will focus on these issues.

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