Clinical Analysis of 670 Cases in Two Trials of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group Subtyped According to the Revised European-American Classification of Lymphoid Neoplasms: A Comparison With the Working Formulation


In the Working Formulation (WF), non-Hodgkin’s lymphomas (NHL) are grouped according to their clinical behavior. These disorders are listed as entities defined by morphology, phenotype, and cytogenticities in the proposed Revised European-American Classification of Lymphoid Neoplasms (REAL), the clinical relevance of which is still debated. We analyzed 670 NHL cases included in two randomized clinical trials (EORTC 20855 WF—intermediate/high-grade and 20856 WF—low-grade malignancy) with histologic material available for review. Based on hematoxylin-eosin—stained sections, 77% of cases could be subtyped. Immunophenotyping was considered to be mandatory only in diagnosing T-cell lymphoma and anaplastic large-cell lymphoma. Of 522 cases subtyped, 11% were mantle cell lymphoma (MCL) 5% were marginal zone B-cell lymphoma (MZBCL), 46% were follicle center lymphoma, and 32% were diffuse large B-cell lymphoma. Statistical analysis and comparisons between classifications were made only within each trial and treatment group. MCL and MZBCL were characterized by a shorter median survival (3.4 and 4.1 years, respectively) in comparison with low- and intermediate-grade WF groups (>9.3 and 5.8 years, respectively). In terms of progression-free survival, MCL showed a behavior similar to the low-grade group, with frequent relapses. Follicle center cell lymphomas behaved as low-grade lymphomas as defined by the WF and diffuse large B-cell lymphomas as the WF—intermediate grade group. Because several NHL entities have a clinical behavior of their own, their recognition by the REAL classification offers clinicians additional information that is not obtained when the WF is used.

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THE TWO MAIN non-Hodgkin’s lymphoma (NHL) classifications currently in use in different parts of the world are the Working Formulation (WF) and the Kiel classification. The former was meant to be a translation system among different classifications and the separation of histologic subgroups into low-, intermediate-, and high-grade categories was based on clinical experience. In contrast, the Kiel classification was based on the putative normal counterpart; grading was based on morphologic features and did not always correlate with clinical behavior. The WF and Kiel classifications have served as the basis for clinical trials on NHL over the last 10 years. Several entities, eg, chronic lymphocytic leukemia, hairy cell leukemia, lymphoblastic lymphoma, Burkitt’s lymphoma, plasmacytoma, and mycosis fungoides, were never included in these clinical studies because they were recognized as unique disorders with a distinctive clinical behavior. This has resulted in the identification of specific and successful therapeutic regimens for these lymphoma entities. Most clinical trials have been designed to address the other NHLs as relatively homogeneous groups of low-, intermediate-, or high-grade malignant diseases, although comprising various distinctive morphologic entities. With the wider use of immunohistochemistry and cytogentic and molecular analysis, new entities have been defined that may share some growth patterns and morphologic features with other entities. A follicular/nodular pattern can be found not only in follicular lymphomas, but also in mantle cell lymphoma (MCL), marginal zone B-cell lymphoma (MZBCL; monocytoid B-cell lymphoma), and even as a pseudofollicular pattern in chronic lymphocytic leukemia (CLL). Although in follicular lymphomas this pattern is associated with a better prognosis, in the other entities (eg, MCL) such correlation has not yet been proven. This correlation has also not been proven in CLL, in which the prognostic significance of a pseudofollicular pattern is still controversial. Within follicular lymphomas there are always difficulties in establishing different subgroups by morphologic criteria, but this distinction is critical in the attribution of follicular lymphomas to low or intermediate categories of the WF. Recently, the International Lymphoma Study Group (ILSG) has proposed a new classification scheme based on a list of disease entities already recognized in the clinical and pathologic practice. This proposal does not group NHL into low-, intermediate-, and high-grade malignancies, but instead promotes the concept that a range of morphologic grades and degrees of clinical aggressiveness might be present within each entity.

To test the clinical validity of this proposal, we reviewed the histologic material of cases from two clinical trials from the Lymphoma Cooperative Group in the European Organization for the Research and Treatment of Cancer (EORTC).
Clinical analysis of NHL based on the REAL

Table 1. Subtyping According to WF and REAL for All Cases Included in Trials 20855-20856

<table>
<thead>
<tr>
<th>Subtyping</th>
<th>20855 Pre-B</th>
<th>Pre-T</th>
<th>20856 Pre-B</th>
<th>Pre-T</th>
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</thead>
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<tr>
<td>WF-A</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>LF-</td>
<td>119</td>
<td>3</td>
<td>4</td>
<td>1</td>
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<td>WF-C</td>
<td>178</td>
<td>4</td>
<td>135</td>
<td>4</td>
</tr>
<tr>
<td>WF-D</td>
<td>28</td>
<td>1</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>WF-E</td>
<td>60</td>
<td>1</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>WF-F</td>
<td>44</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>WF-G</td>
<td>180</td>
<td>6</td>
<td>4</td>
<td>114</td>
</tr>
<tr>
<td>WF-H</td>
<td>41</td>
<td>1</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>WF-I</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>WF-J</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unclass</td>
<td>16</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>28</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>670</td>
<td>4</td>
<td>58</td>
<td>240</td>
</tr>
</tbody>
</table>

Abbreviations: WF-A, small lymphocytic; WF-B, follicular, predominantly small cleaved cell; WF-C, follicular, mixed, small cleaved and large cell; WF-D, follicular, predominantly large cell; WF-E, diffuse, small cleaved cell; WF-F, diffuse, mixed, small and large cell; WF-G, diffuse large cell; WF-H, large-cell immunoblastic; WF-I, lymphoblastic; WF-J, diffuse, small noncleaved; PRE-B/LBL, precursor B-cell neoplasm (precursor B-lymphoblastic leukemia/lymphoma); CLL, B-cell chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FCL, follicle center lymphoma; MZBCL, marginal zone B-cell lymphoma; DBLCL, diffuse large B-cell lymphoma; PRE-T/LBL, precursor T-cell neoplasm (precursor T-lymphoblastic leukemia/lymphoma); PTCL, peripheral T-cell lymphoma—unspecified; AILD, angioimmunoblastic T-cell; AIL, angiocentric lymphoma; ALCL, anaplastic large-cell lymphoma; T- and null-cell type; ALCL/HD, anaplastic large-cell lymphoma, Hodgkin’s like; Uncl poor, unclassifiable due to poor quality; Uncl, unclassifiable.

Materials and methods

Patient selection. Patients were entered in two randomized clinical trials (EORTC 20855-20856) between 1985 and 1991. Patient selection and eligibility criteria were previously described. Briefly, selection criteria for trial 20855 included the following: age between 15 and 70 years, a performance status (PS) of 0 to 2, an Ann Arbor stage of II to IV, and primary nodal or Waldeyer’s ring involvement. In the two treatment arms the patients received either eight cycles of cyclophosphamide, doxorubicin, teniposide (VM26), prednisone, vincristine, and bleomycin (CHV-MOPP), or modified doxorubicin, cyclophosphamide, etoposide (VP16), mechloretamine, vincristine, procarbazine, and prednisone (ProMACE-MOPP); additional radiotherapy was administered at sites of initial large masses or residual disease after three courses. In the CHV-MOPP treatment arm, cyclophosphamide (600 mg/m²), and doxorubicin (50 mg/m²) were administered by an intravenous (IV) push injection on day 1; VM26 (60 mg/m²) was administered in a slow-running IV drip over 1 hour on day 1. Prednisone was administered orally at a dose of 40 mg/m² on days 1 through 5. On day 15, vincristine (2 mg total dose) and bleomycin (10 mg total dose) were administered by IV push. The next course started on day 21. In the ProMACE-MOPP scheme, doxorubicin (25 mg/m²), cyclophosphamide (650 mg/m²), and VP16 (120 mg/m²) were administered on day 1; mechloretamine (6 mg/m²) and vincristine (1.4 mg/m²) were administered on day 8 IV. Procarbazine (100 mg/m²) on days 8 through 15 and prednisone (60 mg/m²) on days 1 through 15 were administered orally. For trial 20856, the inclusion criteria were the following: more than 15 years of age, untreated low-grade (WF) NHL, a PS of 0 to 2, and an Ann Arbor stage of III to IV. As therapy, these patients received 8 induction cycles with cyclophosphamide (300 mg/m²), vincristine (1.4 mg/m²), and prednisone (40 mg/m²) orally on days 1 through 5 (CVP); iceberg radiotherapy was administered in case of slow response or initial bulky disease. Patients were randomized to receive maintenance treatment with interferon-α-2a (3 × 10⁶ IU) by subcutaneous injection every week for 1 year or no further treatment. Patients with a diagnosis of small lymphocytic (WF-A), lymphoblastic (WF-I), and small noncleaved (WF-J) NHL were excluded from these trials.

Pathology review. Of the 777 patients enrolled in both trials, incomplete data from 58 cases were received. Randomization in both trials was based on the pathology report as issued by the individual participating centers. The histologic sections from 719 patients were originally reviewed by one of us (C.D.W.-P.) for the EORTC Lymphoma Cooperative Group and classified according to the Working Formulation during the course of the trial. This subclassification was taken as such in the present study. Slides of 49 cases from both trials were returned to the original hospitals immediately after central review and therefore were not available for the present study. The remaining slides from 670 patients were recently reviewed by two of us (C.D.W.-P. and S.P.) and reclassified according to the REAL. This review was based on hematoxylin-eosin (H&E)-stained sections. Immunophenotyping data were available in 481 cases (71%); of these, 313 were analyzed on paraffin sections (65%; 48 performed during the revision), 167 were analyzed on frozen sections (35%), and only 1 case was analyzed using flow cytometry. Except for the cases in which immunostains were performed during the revision, for all other cases the data were taken from the local pathology forms and reports. If the final diagnosis was not confirmed by immunophenotyping or there was disagreement between the two reviewers, the case was considered unclassifiable.

Grading of follicle center cell lymphoma (FCL) was performed according to the modified Mann and Berard approach as outlined by Jaffe et al. Briefly, if the majority of follicles were composed...
of small cleaved lymphoid cells with fewer than five large non-cleaved cells per follicle, it was considered to be grade 1. If the number of large non-cleaved lymphoid cells per follicle was at least 5, it was grade 2. Only when the predominant cells were large non-cleaved was it considered to be grade 3. In addition, the degree of nodularity was considered; if it was ill-defined with predominant diffuse areas, the cases were considered to be grade 3.

**Statistical analysis.** Statistical analyses were performed on 642 cases; slides were reviewed and classified according to the WF and the REAL and included only cases that were classified under both schemes. The comparisons were made between the WF subgroups (low and intermediate) and the five following categories of the proposal: MCL, FCL, MZBCL, diffuse large B-cell lymphoma (DLBCL), and anaplastic large-cell lymphoma of null or T-cell phenotype (ALCL). No other subtypes were analyzed because of the small number included in the study. Overall survival was calculated from the study entry date until death from any cause. Patients alive at the time of analysis were censored at their last follow-up date (December 1994). Progression-free survival was calculated from the entry date until first progression or relapse was reported. Comparisons between categories were made only within a trial and treatment group, following the basic compare like with like principle. The statistical differences between trials and treatment assignment were taken into account by stratifying for those characteristics. Within each separate stratum, observed minus expected (O-E) numbers of events and their variance (V) were calculated using a log-rank test. The overall results were assessed by adding up the totals of the O-E and the V over all stratification levels. Survival curves were estimated using the Kaplan-Meier method. All P values referred to are two-sided. The dispersion of failure times for each pathologic category was studied using the 95% confidence intervals at the median and the 75th percentile. These intervals were calculated by the reflection method. To compare time to events for ordered categories, we used a test for trend.

**RESULTS**

**Pathology data.** All cases diagnosed according to the WF subtypes are listed for both trials combined (Table 1). The unclassified group included cases that could not be subtyped according to the WF. The missing group comprised cases for which the WF was lacking in the original central review form.

Histologic revision of all available cases, adopting the criteria of Harris et al. is shown in comparison with the WF categories (Table 1).

MCL comprised 58 cases, of which 30 were from the WF-E (60 cases total) and 19 were from the WF-B (119 cases total). Although a vague nodular pattern could be seen in most of the cases from the latter group, a definite mantle zone pattern was observed in only 2 cases. A blastic variant was observed in 1 case. All other cases showed typical features of MCL, with a diffuse monomorphic proliferation of medium-sized lymphoid cells with slightly irregular nuclei and scanty cytoplasm.

FCL comprised 240 cases, most of them within the follicular WF categories B through D. Thirteen cases diagnosed as FCL were from the WF-E (60 cases total) and 19 were from the WF-B (119 cases total). Although a vague nodular pattern could be seen in most of the cases from the latter group, a definite mantle zone pattern was observed in only 2 cases. A blastic variant was observed in 1 case. All other cases showed typical features of FCL, with a diffuse monomorphic proliferation of medium-sized lymphoid cells with slightly irregular nuclei and scanty cytoplasm.

**Table 2. Baseline Characteristics of All NHL Patients Subtyped According to the WF and the REAL**

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<tr>
<th></th>
<th>WF-ABC</th>
<th>WF-DEFG</th>
<th>WF-HJ</th>
<th>MCL</th>
<th>FCL</th>
<th>MZBCL</th>
<th>DLBCL</th>
<th>ALCL</th>
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<tr>
<td>%</td>
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<td>47</td>
<td>8</td>
<td>11</td>
<td>46</td>
<td>5</td>
<td>32</td>
<td>2</td>
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<td>17-73</td>
<td>33-91</td>
<td>19-80</td>
<td>39-77</td>
<td>17-70</td>
<td>25-65</td>
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<td>Median age (yr)</td>
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<td>56</td>
<td>51.5</td>
<td>57.5</td>
<td>50</td>
<td>57</td>
<td>52</td>
<td>41</td>
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<td>Sex ratio (M:F)</td>
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<td>1.25</td>
<td>3.8</td>
<td>0.95</td>
<td>1</td>
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<td>89</td>
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<td>trephine (%)</td>
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<td>Hepatomegaly (%)</td>
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<td>Splenomegaly (%)</td>
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<td>19</td>
<td>10</td>
<td>20</td>
<td>11</td>
<td>33</td>
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</table>

The total number of cases for WF is 667 (percentage of low, intermediate, and high calculated over 667) for the REAL the total number of cases subtyped is 522 (percentage calculated over 522, which includes T-cell types and others). The number of cases for each group is in parentheses. All percentages refer to number of positive cases.
the morphologic heterogeneity of this entity, which is composed of centrocyte-like cells, blast-like cells, and plasma cells in either a parafollicular or a diffuse growth pattern with and without colonization of the follicle center.

Of the 165 cases diagnosed as DLBCL, the majority originated from the WF-G. The second largest contributing subgroup was large-cell immunoblastic lymphoma (WF-H). A considerable morphologic variability regarding the cytologic characteristics of the neoplastic cells was observed, ranging from a monotonous population to a very polymorphic one; the associated stromal reaction was also variable, ranging from a minimal reaction to large number of T cells or histiocytes.

T-cell lymphomas (20 cases), which could be identified by morphology and confirmed by immunophenotype, were previously classified as diffuse mixed (WF-F; 8 cases). Of the 12 cases of ALCL, 7 were in the unclassified WF group. Seventy-four cases from both trials were not subtyped due to poor quality (ie, fixation artifacts) or inadequate material. An additional 74 cases could not be subtyped due to insufficient criteria to fit one specific category (borderline characteristics) or due to the presence of overlapping features between categories. Of these cases, 31% were in the unclassified small cell categories and the remaining were in the unclassified large-cell categories. The markers available on paraffin section were not sufficient to resolve all diagnostic difficulties. However, most of these cases might have been subtyped if phenotyping on frozen material was available. Immunophenotyping data were mainly useful in cases in which follicular lymphoma had to be differentiated from follicular hyperplasia and in the
diagnosis of T-cell lymphoma (including ALCL). In the latter, only cases documented by phenotyping data supporting the histologic diagnosis were taken into consideration. All others were indicated as unclassifiable. Overall, the histologic diagnoses were modified in 4% of cases after immunophenotyping; this occurred in the attribution of B phenotype versus T phenotype.

Clinical data. Clinical characteristics of the five main categories represented (MCL, MZBCL, FCL, DLBCL, and ALCL) in comparison with the low-grade (WF-ABC), intermediate-grade (WF-DEFG), and high-grade (WF-HI) subgroups are shown in Table 2. The age range was similar among all groups except for the ALCL, which included patients 10 years younger (median age 41 years v 50 to 57.5 years in all other categories). There was a male predominance in MCL and ALCL. The number of patients with stage IV disease was higher in the first three groups. Extranodal cases at presentation were seen most frequently in the MZCL group, with 6 cases (24%) localized to parotid (1 case), stomach (2 cases), Waldeyer’s (1 case), stomach + Waldeyer’s (1 case), and soft tissue (1 case), respectively. Of these patients, all but 1 were stage III-IV. In the DLBCL group, 23 cases (14%) had an extranodal presentation; 2 cases in MCL (3%) and 4 in the FCL group (1.6%) also had an extranodal presentation. Because of their small number, the extranodal cases were not considered to be a separate group. Bone marrow involvement assessed by trephine biopsies was found most frequently in MCL patients followed by FCL, MZBCL, and in DLBCL or ALCL, in which it is rarely seen. Using bone marrow smear, the number of posi-
tive cases was less in the first three categories and ALCL, whereas it was unchanged for DLCBL. Systemic symptoms were most frequently observed in ALCL patients. Liver and spleen enlargement were present in comparable percentages in all groups.

When comparing the MCL group versus WF-ABC in a test stratified by study (trial 20855 and 20856) and by treatment (4 treatments and a nontreated group), there was a significant difference in overall survival ($P = .02$; Fig 1A), with a median survival of 3.4 years for MCL versus greater than 9.3 years for WF-ABC. No significant difference was observed in terms of progression-free survival (Fig 1B). In comparing the same MCL group versus WF-DEFG, no significant difference was observed in terms of overall survival (Fig 1A), but the progression-free survival was significantly different ($P = .01$), with more frequent relapses in the MCL cases (Fig 1B).

Although no significant differences were observed in the comparison of the MZBCL with the WF-ABC and WF-DEFG, their survival curve showed a steeper slope than the low-grade lymphomas, with a median survival of 4.1 years versus greater than 9.3 years for WF-ABC (Fig 2A). Regarding progression-free survival, the MZBCL curve had a sharp decline within the first 2 years; however, the long-term behavior could not be assessed due to the small number of cases and relatively short follow-up (Fig 2B).

The FCL category, defined by the REAL as one entity, behaved as a low-grade disease as defined by the WF (median survival of 7.8 years and frequent relapses); although most of the patients belonged to the WF-BC, cases were also present
throughout the other WF groups (WFA-G; see Table 2). When the cases were analyzed by grading, although no difference was observed among the three groups (grades 1, 2, and 3) in terms of survival (test for trend $P > .1$), progression-free survival was shorter for the grade 3 with respect to grades 2 and 1 (test for trend $P = .03$; Fig 3A and B).

In terms of behavior, the DLBCL reflected the corresponding categories of the WF (DEFG). No differences were observed in terms of survival or progression-free survival also when compared with WF-F, -G, and -H (Fig 4A and B).

Combining all the T-cell lymphomas, the overall behavior was similar to the intermediate categories, although the median survival was shorter in this group when compared with the WF-F, -G, and -H, ie, 3.2 years for TCL versus 5.19 years for WF-F, -G, and -H (Fig 5A and B).

To analyze the heterogeneity within each entity, using reflected confidence interval at the median survival time based on censored data (Table 3), we could make the following additional observations. In terms of survival at the median, the dispersion (which is represented by $\Delta$ values) in MCL, MZBCL, and FCL was relatively narrow in comparison with DLCBL, suggesting that the former disorders represent a more homogeneous group of patients. At the 75th percentile, the behavior of these NHL did not differ with similar $\Delta$ values for MCL, FCL, and DLCBL. In MZBCL, the relatively wide range observed could be explained by the small number of cases or could reflect the biologic behavior of the disease. Regarding progression-free survival, the behavior of MCL is similar to the FCL, whereas DLBCL and MZBCL share a wider range at the median; by contrast,
the dispersion at the 75th percentile is relatively narrow for all categories analyzed (Figs 4 and 5).

**DISCUSSION**

Most clinical trials on NHL are based on the WF. Except for some well-characterized entities, other NHLs are subgrouped into 3 or, in most situations, into 2 categories, ie, low-grade and intermediate/high-grade malignant disorders. The heterogeneity of the various lymphoma entities included in these groups may be therefore lost.4,18,19 In the recent proposal,10 lymphoma entities are recognized based on their morphology, phenotype, and cytogenetics and are listed as such without being grouped.

In 670 NHL cases from two EORTC clinical trials, subtyping according to the REAL was achieved in 75% of cases based in most of them exclusively on H&E. In most of the cases the phenotyping data were in line with the histologic diagnosis. In only 4% of the cases were the diagnoses modified by immunophenotypical data, eg, a T-cell lymphoma diagnosis by morphology not supported by immunostains was changed. In 11% of cases subtyping was not possible due to incomplete phenotypic data available and in some cases due to morphologic features overlapping among different entities.

Fifty-eight cases previously diagnosed in the WF-B through -E subgroups were presently recognized as MCL (11%). In terms of clinical presentation, a preponderance of male patients and a more frequent bone marrow involvement were found in comparison with the WF subgroups. Furthermore, the overall survival and progression-free survival were
significantly worse than for patients in the WF-ABC and DEFG (Figs 1A and 2B), respectively. None of the therapeutic regimens used in these trials had a significant effect on survival or progression-free survival.12

The MZBCL cases, which histologically were widely distributed among the WF subgroups, represented 5%. Clinically, median age, sex, and bone marrow involvement were similar to the WF-DEF category and there was a more frequent extranodal involvement (24%) at presentation than in other categories despite the inclusion criteria of both trials (ie, nodal disease). By staging and by clinical behavior, these cases did not differ from the other MZCL. For these reasons and because of their small number, the distinction between MALT and monocytoid B-cell lymphoma was not taken into account. There was no significant difference in terms of behavior when compared with low-grade and intermediate-grade NHL, and we can only notice that half of the patients died even with this relatively short follow-up. In terms of progression-free survival, there was a tendency for more frequent relapses and shortest for WF-B? Moreover, more durable remissions are achieved in the WF-C group compared with WF-B,21 suggesting that biologic differences may play a role. In European trials, the prognostic significance of these subgroups has not been confirmed.22 These discrepancies can be explained by the absence of uniform pathologic criteria as well as by the inclusion of MCL and MZBCL in the WF-B group. It is of interest to note that, using the reflected interval analysis, FCL, as defined in the REAL, represents, as does MCL, a relatively homogeneous entity. Using the same analysis, MZBCL and DLBCL are still heterogeneous, suggesting that these categories may show wider clinical heterogeneity or may include several entities not yet defined.

T-cell lymphomas in these two trials represented 3.8% of the cases and 12 cases could be identified as ALCCL null or T-cell type. The latter mainly affected male patients in their forties. Overall survival and progression-free survival in the present study were similar to the WF intermediate category (Fig 5A and B). The low number of T-cell lymphomas could reflect the known lower incidence of this cell type in European countries in comparison with Asian countries24 and could also be affected in part by the presence of cases with an incomplete immunophenotype.

In summary, subtyping NHL according to the REAL offers the clinician additional information to the WF because it allows the identification of entities with a distinct clinical behavior. One may expect that, as for other specific NHLs, a more accurate definition of the various lymphoma entities might allow the design of more appropriate therapies for each one of them with a better chance of success.

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Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the Revised European-American Classification of Lymphoid Neoplasms: a comparison with the Working Formulation

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