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Clinical Features and Treatment Outcomes of Grey Zone Lymphoma (GZL), Unclassifiable B-Cell Lymphoma with Features Intermediate between Diffuse Large B-Cell Lymphoma and Classical Hodgkin Lymphoma - a Real-Life Multicenter Study By the Croatian Cooperative Group for Hematologic Diseases (KroHem)

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GZL with features between classical Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) is a rare entity originally introduced in the 2008 World Health Organization (WHO) classification. GZL has been included in KroHem Lymphoma Treatment Guidelines since 2012. The recommended treatment was induction with escalated BEACOPP (escBEACOPP) in those below 60 y and ABVD in those above 60 y, both in combination with rituximab (R) and consolidation with radiotherapy (RT) for patients with limited or autologous stem cell transplantation (ASCT) in those with advanced-stage disease.

We conducted a comprehensive retrospective analysis of GZL patients treated in KroHem centers to evaluate clinical features, treatment outcomes and prognostic factors.

GZL diagnoses were confirmed by a hematopathologist from a designated expert center, according to current WHO classification at time of diagnosis.

Twenty-three patients were evaluable for analysis, 20 diagnosed *de novo*, and 3 in relapse (2 after HL, 1 after DLBCL). Fourteen patients (60%) were male; median age was 39 and range 18-78 y. Thirteen (57%) presented with mediastinal GZL (MGZL) and 10 (43%) with non-MGZL (NMGZL). NMGZL patients were older (median 55 versus 31 y, $p = 0.0157$) and had more frequently high NCCN-IPI scores (9/10 vs 5/13, $p = 0.0288$). Twelve front-line patients received R-escBEACOPP, 4 DA-R-EPOCH, 1 R-ABVD and 3 R-CHOP-like regimen. Of the 3 patients diagnosed in relapse, 2 were treated with R-ICE and 1 with R-CHOP. Ten patients were irradiated and 9 underwent ASCT as consolidation in 1 st remission. Stem-cell collection was successful in all planned patients, albeit 70% with plerixafor.

Sixteen (80%) front-line patients responded to immunochemotherapy, 2 progressed during consolidation. At the end of treatment, 13 patients were in complete and 1 in partial remission for a response rate of 70%. Of the 3 relapsing patients, 2 treated with R-ICE responded, underwent ASCT and are in continuous remission. One patient died of toxicity after ASCT in 1 st remission.

After a median survivors follow-up time of 42 months, 6 front-line patients have died and additional 3 progressed. Overall survival (OS) at 4 y is 65% and event-free survival (EFS) 52%. MGZL and NMGZL patients had similar outcomes; OS at 4 y was 69% and 64% (p=0.637) and EFS 52% vs. 50% (p=0.88) respectively. Performance status was a statistically significant prognostic factor (OS at 4 y ECOG grade 0-1 90% vs. ECOG grade 2-4 17%, p<0.001; EFS at 4 y 67% vs. 17% p=0.044). Sex influenced EFS (male 70%, female 33% at 4 years, p=0.050), but not OS (69% vs. 61% p=0.667). Age (< 60 y >), presence of bulky or extranodal disease, stage, anemia, LDH or B2M level did not significantly influence outcomes. Patients treated with R-escBEACOPP had numerically superior outcomes (OS at 4 y 81% vs. 44%, p=0.167; EFS at 4 y 64% vs 38%, p=0.293). Despite the small number of patients, the difference was statistically significant in patients with MGZL; EFS at 4 y was 71% in the group treated with R-escBEACOPP vs 0% in the group treated with other regimens (p=0.021) and OS 100% vs. 0% (p<0.001). In contrast, patients with NMGZL treated with R-escBEACOPP had numerically inferior outcomes in comparison to those treated with other regimens (p=0.127 for OS and p=0.388 for EFS).
In conclusion, our data confirm the validity of differentiating between MGZL and NMGZL. MGZL patients might benefit from aggressive therapies designed for HL, such as escBEACOPP, in combination with rituximab. Consolidation with ASCT is feasible, but most patients will need plerixafor to collect sufficient stem cells. Different regimens, as used for DLBCL, should be preferred in NMGZL patients.

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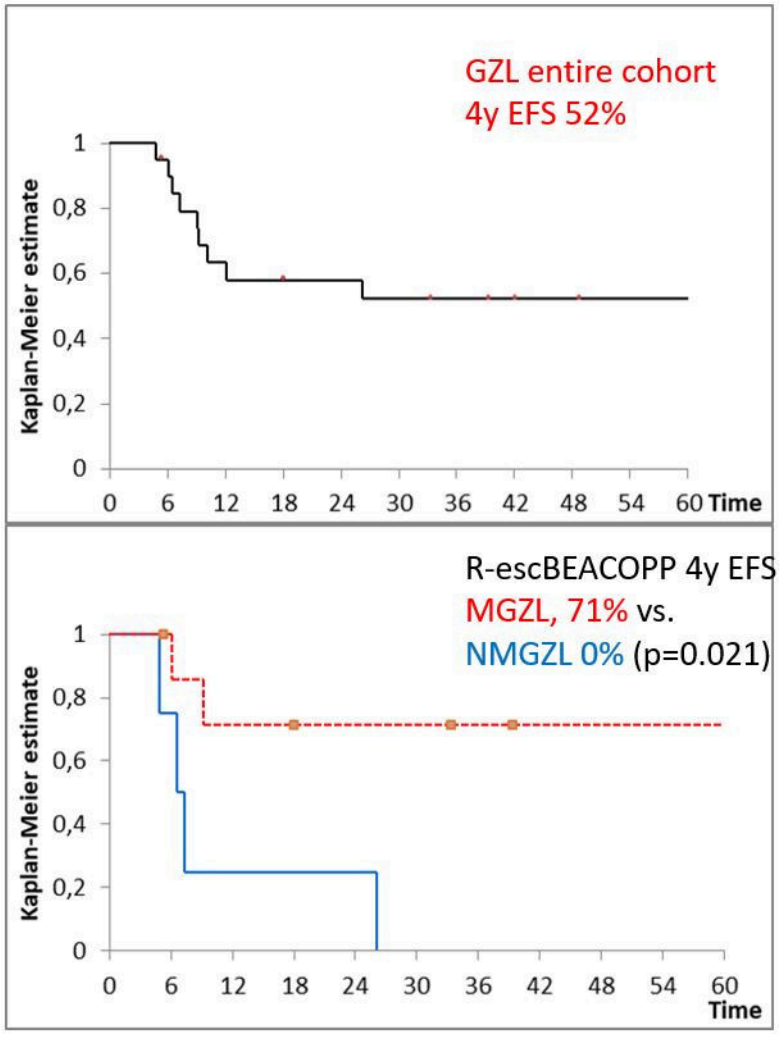

Figure 1

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