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Dose adjusted-EPOCH-R and mediastinal disease may improve outcomes for patients with Grey Zone Lymphoma

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Grey zone lymphoma; ABVD; EPOCH; treatment

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, also known as grey zone lymphoma (GZL), is typically associated with mediastinal disease and shares clinical, morphological and immunophenotypic features of classical Hodgkin lymphoma (CHL) or primary mediastinal B-cell lymphoma (PMBL) (Quintanilla-Martinez and Fend 2011, Swerdlow, *et al* 2008, Traverse-Glehen, *et al* 2005). Mediastinal GZL is often aggressive and resistant to chemotherapy, and patients have worse outcomes than patients with either CHL or PMBL (Traverse-Glehen, *et al* 2005, Wilson, *et al* 2014). However, given the rarity of the diagnosis and the overlapping pathological features, there is much heterogeneity in the treatment strategies utilized.

We retrospectively analysed 16 patients diagnosed with GZL between 2007 and 2014 at MD Anderson Cancer Center. The diagnosis of GZL was established according to the criteria stated in the fourth edition of the World Health Organization classification (Swerdlow, *et al* 2008), and was confirmed by the pathologist at our institution. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method (Kaplan and Meier 1958), and groups were compared using the log-rank test. Candidate prognostic factors for PFS and OS were evaluated by Cox regression analysis. All analyses were performed using STATA version 13.1 (StataCorp LP, College Station, TX), with the

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Contributions: D.C., M.F., R.S. designed the study. D.C. performed the statistical analysis. J.R.W., R.N.M., C.Y.C., Y.O., F.T., J.R., S.S.N., L.J.N., L.F., A.R., N.H.F., R.Z.O., M.W., F.B.H., L.J.M. provided cases. D.C. and M.F. interpreted the data and wrote the draft of the paper. All authors have read and approved the final version of the manuscript.

significance level set at 5%. The study was performed in accordance with the declaration of Helsinki and approved by the institutional review board of MD Anderson Cancer Center.

Median age of the cohort was 39 years (range, 19-64) (Table I). Twelve patients had an International Prognostic Index that was low (11 patients) or low-intermediate (1 patient); four patients were not evaluable due to lack of data. Six patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), three received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), five received DA-EPOCH-R (dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) (Wilson, *et al* 2014) and two received R-HCVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine) (Romaguera, *et al* 2005). There were no significant differences in background characteristics among patients who received different treatments, although with small numbers. Five patients (2 DA-EPOCH-R, 3 R-CHOP) received consolidative radiotherapy (RT) after first-line chemotherapy. All patients had response evaluation by positron emission tomography (PET) scan; 11 achieved complete response (CR, 69%), three had disease progression (19%) and two had stable disease (12%). Of note, all patients who received DA-EPOCH-R and R-HCVAD/MA achieved CR (100%), whereas the patients who received R-CHOP and ABVD had lower CR rates of 50% and 33%, respectively. With a median follow up of 32.2 months, nine patients experienced relapse and two died of progression. Five of the nine patients who relapsed underwent autologous stem cell transplant after salvage therapy with a median number of 3 (range, 2-4) chemotherapy regimens. All patients were CD30 positive and five patients received brentuximab vedotin after relapse (3 in 3rd-line and 2 in 4th-line), but only one achieved CR and the other four had progressive disease. The median PFS and OS was 16.8 months and not reached, respectively. The overall 2-year PFS and OS was 42% and 93%, respectively. Patients who received DA-EPOCH-R had a significantly longer PFS than patients who received R-CHOP, R-HCVAD/MA or ABVD (Figure 1A). However, there were no differences in OS (Figure 1B). The 2-year PFS for patients who received R-CHOP or R-HCAVD/MA, ABVD and DA-EPOCH-R was 25%, 0% and 100%, respectively. Multivariate analysis revealed that patients with mediastinal disease had significantly longer PFS than patients who do not (Hazard ratio [HR]: 0.1, 95% confidence interval [CI]: 0.01-0.99).

In this study, DA-EPOCH-R showed excellent clinical outcomes with both CR rate and 2-year PFS (100%), although with a short follow-up. Notably, a prospective study analysing DA-EPOCH-R for 24 patients with mediastinal GZL showed a 100% response rate (CR rate: 79%). However, 9 patients relapsed early (all within 6 months) and the event-free survival (EFS) and OS were 62% and 74%, respectively, with a median follow-up of 59 months (Wilson, *et al* 2014). The study included higher risk patients than the current study, including a higher proportion of patients with an elevated lactate dehydrogenase and bulky disease. Also, RT was not included in the protocol so that the initiation of RT was considered as an event, which is a different definition to PFS in the current study. Of note, Wilson *et al* (2014) were able to salvage 4 of 9 patients who had PET-positive mediastinal disease with RT, suggesting a role for RT, especially for residual disease. Although the outcome of DA-EPOCH-R for patients with mediastinal GZL was inferior to the outcome for patients with primary mediastinal B-cell lymphoma (Dunleavy, *et al* 2013), DA-EPOCH-R has shown the

best benefit for this diagnosis to date. The role of RT remains controversial and should be evaluated in a prospective clinical trial.

Recently, a large multicentre retrospective study reported the outcome of 112 patients with GZL (Evens, *et al* 2015), in which DA-EPOCH-R showed a trend for prolonged PFS (HR: 0.34, $P=0.07$), and ABVD was significantly associated with shorter PFS (HR: 1.69, $P=0.04$), findings similar to the current study. Interestingly, that study included a higher number of non-mediastinal GZL (64/112 patients, 57%) and those patients had higher risk factors than patients with mediastinal GZL, such as significantly older age, more often had bone marrow involvement and extranodal involvement, and presented with advanced stage disease, eventually having higher IPI risk factors. However, there was no significant difference in survival outcome between non-mediastinal GZL and mediastinal GZL. We found that the patients with mediastinal GZL had a significantly longer PFS, although with very small number of patients. These observations potentially suggest differences in the tumour biology of mediastinal versus non-mediastinal GZL, and further studies are desired.

In conclusion, our data suggest that DA-R-EPOCH may improve outcomes for GZL patients. A large multicentre prospective trial is needed to best define optimum therapy, and a better understanding of the unique molecular features of this rare diagnosis is critical to further refine the treatment strategies, particularly for guiding a rationale selection of targeted therapeutics.

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Figure 1.

A. Progression-free survival according to treatment

B. Overall survival according to treatment

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; DA-EPOCH-R, dose-adjusted etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-HCVAD/MA, rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine.

Table I

Patient characteristics

		n (%)
Total number of patients		16 (100)
Age, years: median (range)		39 (19-64)
Male		8 (50)
Performance status	2-4	2 (13)
Stage	3-4	6 (38)
B symptoms at diagnosis	Present	6 (40)
Mediastinal mass	Present	12 (75)
Bone marrow involvement	Present	1 (6)
Bulky disease	10 cm	4 (31)
Lactate dehydrogenase	> Upper normal limit	1 (11)
Extranodal involvement	> 2	1 (7)
International prognostic index	High-Intermediate, High	0 (0)

All values given as n (%) unless stated otherwise.