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Retrospective analysis of primary gastric diffuse large B-cell lymphoma: a single center study from Turkey

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Background/aim: Diffuse large B-cell primary gastric lymphomas (DLBC-PGLs) are treated with different therapies. Their optimal treatment is not well documented.

Materials and methods: We retrospectively analyzed the data of 51 patients diagnosed with DLBC-PGL in the previous 10 years. All patients were treated with R-CHOP as first line. Radiotherapy was added to chemotherapy in 8 patients. Surgery was performed in 5 patients.

Results: The median follow-up time of the 51 patients was 45.5 (range 5–144) months and the complete response (CR) rate was 90.2%. CR was achieved in 34 (89.4%) of 38 patients treated with single chemotherapy, in all (100%) 5 patients treated with chemotherapy plus surgery, and in 7 (87.5%) of 8 patients treated with chemotherapy plus radiotherapy. The 5-year overall survival (OS) and event-free survival (EFS) rates were 85.8% and 89.6%, respectively. The 5-year OS and EFS rates were not significantly different between patients treated with single chemotherapy or chemotherapy plus radiotherapy/surgery ($P > 0.05$).

Conclusion: R-CHOP chemotherapy is as effective as R-CHOP plus radiotherapy/surgery in the treatment of DLBC-PGL patients. Prospective randomized large cohort studies are needed to generate guidelines for the treatment of DLBC-PGL.

Key words: Lymphoma, diffuse large B cell, gastric, chemotherapy, radiotherapy, surgery

1. Introduction

Primary non-Hodgkin lymphomas (NHLs) of the gastrointestinal system (GIS) are rare entities that account for only 1%–4% of all gastrointestinal malignancies. The stomach is the most common site. Patients typically present with nonspecific signs and symptoms like abdominal pain, weight loss, and, less commonly, gastrointestinal hemorrhage (1). Low grade mucosa associated lymphoid tissue (MALT) lymphoma and high grade diffuse large B-cell lymphomas are the most common histological subtypes (2).

Chemotherapy, radiotherapy, surgery, and combinations of these modalities are used for the treatment of diffuse large B-cell primary gastric lymphomas (DLBC-PGL). In the era of effective chemotherapeutic agents, surgery is only performed in patients with complications like perforation and massive hemorrhage that cannot be taken under control with supportive care (3,4). Survival rates are quite good with combination therapies consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) (5–8).

After reports documented that addition of rituximab, an anti-CD20 monoclonal antibody, to CHOP chemotherapy increased the survival rates in patients with nodal DLBCL, R-CHOP chemotherapy was also accepted as first-line treatment in DLBC- PGL (9–11). However, there are contradicting data in retrospective studies for the effectiveness of rituximab in DLBC-PGL patients. Although complete response (CR), disease-free survival (DFS), and overall survival (OS) rates increased with the addition of rituximab to combination chemotherapies in some retrospective studies, its positive impact could not be demonstrated in other studies (10–15).

In the light of these findings, the optimal treatment for DLBC-PGL remains unclear. Therefore, we performed a retrospective analysis of 51 patients with DLBC-PGL who were treated with single chemotherapy (R-CHOP) or chemotherapy plus radiotherapy or surgery in the previous 10 years.

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2. Materials and methods

We retrospectively analyzed 51 patients (28 female and 23 male) diagnosed with DLBC-PGL between June 2003 and June 2013 in Ege University Hospital Pathology Department. Ethics Committee approval was obtained from the Ege University Ethics Committee (date 15 April 2015, number 15-2.1/3). Data of the patients (age, sex, time of diagnosis, signs and symptoms at diagnosis, stages, treatments, responses to treatments, international prognostic indices, and follow-up periods) were retrieved from the archives of the Hematology and Pathology departments. Endoscopic biopsies were performed in all patients but diagnosis was confirmed with partial gastrectomy in 4 patients because of insufficient biopsy material. The histopathological diagnosis was established according to the WHO classification (16). Bone marrow biopsy and imaging modalities such as positron emission tomography combined with computed tomography (PET/CT) or computed tomography (CT) were used for staging. The Lugano Staging System (stage I–IV) was used for staging of the patients at the time of diagnosis (17). The localized stage was defined as stage I/II1. Performance status of the patients was recorded according to Eastern Cooperative Oncology Group (ECOG) performance status. Laboratory findings were characterized by decreased hemoglobin levels (for women <12 g/dL and for men <13 g/dL) and elevated lactate dehydrogenase (LDH) levels (>225 U/L). All the patients were treated with R-CHOP [(cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (maximum dose of 2 mg) on day 1, prednisolone 100 mg for 5 days, and rituximab 375 mg/m^2 on day 1; every 21 days] as first-line treatment. Involved-field radiotherapy (IFRT) was delivered to some of the patients with localized-stage DLBC-PGL after R-chemotherapy as consolidation or if there was local residual disease. The response to treatment was evaluated according to International Workshop Criteria (18). Complete response (CR) was defined as the disappearance of all lesions and radiological or biological abnormalities observed at the time of diagnosis and absence of new lesions. Partial response (PR) was defined as regression of all measurable lesions by >50%, disappearance of nonmeasurable lesions, and absence of new lesions. Progressive disease (PD) was defined as the appearance of new lesions, growth of the initial lesions by >25%, or growth of any measurable lesion that had regressed during treatment by >50% at its smallest dimension. Stable disease (SD) was neither PR nor PD.

ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) or ICE (ifosfamide, etoposide, and carboplatin) was used as salvage chemotherapy. The conditioning regimen was included BCNU, etoposide, cytarabine, and melphalan (BEAM).

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up or death from any cause. Event-free survival (EFS) was calculated from the date of diagnosis, and patients were censored at the last follow-up visit if they were free of disease. Death (only disease specific deaths were counted as an event), documented disease progression or relapse, or other events, including documented failure of treatment unrelated to disease progression, were considered events.

2.1. Statistical analysis

Quantitative data were expressed as median (range) while qualitative data were expressed as number of cases and percentages. Duration of EFS and OS were estimated according to the Kaplan–Meier method. The effects of clinical variables (IPI score, B symptoms, age, sex, LDH level, hemoglobin level, tumor stage, treatment modality, performance status, response rates, and presence or absence of relapses) on EFS and OS were assessed by univariate analysis. The log-rank test was used to compare curves for the univariate analysis. All analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

3. Results

The median follow-up time of the 51 patients was 45.5 (range 5–144) months. The characteristics of the patients are shown in Table 1. The presenting symptoms of the patients were epigastric discomfort in 42 patients (82.4%), loss of appetite in 13 patients (25.5%), weight loss in 11 patients (21.6%), and nausea and vomiting in 17 patients (33.3%). The corpus and antrum of the stomach were the predominant sites of DLBC-PGL (Table 1). Concurrent low-grade lymphoma was detected only in one patient.

All patients were treated with R-CHOP as first-line treatment. Radiotherapy was also added to chemotherapy in 8 patients as first-line treatment. Surgery was performed in one patient for perforation and in four patients for diagnostic purposes.

We achieved CR in 46 (90.2%) patients of all stages with first-line treatment. CR was observed in 33 (94.3%) of 35 patients at early stages and in 13 (81.2%) of 16 patients at late stages. According to treatment, CR was achieved in 34 (89.4%) of 38 patients treated with single chemotherapy, in all (100%) 5 patients treated with chemotherapy plus surgery, and in 7 (87.5%) of 8 patients treated with chemotherapy plus radiotherapy.

Five patients achieved PR after first-line therapy. All patients with PR were treated with second-line salvage chemotherapy. After therapy, two of the 5 patients achieved CR, two of the 5 patients had SD, and 1 patient died because of PD.

Five patients who achieved CR with first-line treatment relapsed after a median of 17 (range 11–66) months. All

Table 1. Characteristics of the patients.

Number of patients	51
Age (median, range, years) ≤60 >60	65 (21–81) 29 (56.9%) 22 (43.1%)
Sex (female/male)	28/23
Primary gastric site Corpus Antrum Fundus Cardia	 24 (47%) 22 (43.1%) 3 (5.9%) 2 (4%)
ECOG Performance status <2 ≥2	 48 (94.1%) 3 (5.9%)
Lactate dehydrogenase (U/L) Normal (135–225) >225	 35 (68.6%) 16 (31.4%)
Hemoglobin normal low	 17 (33.3%) 34 (66.7%)
Lugano staging system Stage < II2 Stage ≥ II2	 35 (68.6%) 16 (31.4%)
B symptoms Yes No	 17 (33.3%) 34 (66.7%)
IPI score 0–2 3–5 (high)	 44 (86.2%) 7 (13.8%)
First-line treatment Chemotherapy (R-CHOP) Chemotherapy + radiotherapy Chemotherapy + surgery	 38 (74.5%) 8 (15.7%) 5 (9.8%)

were treated with second-line salvage chemotherapy. Three of the 5 patients achieved CR and one patient achieved PR. One patient died because of sepsis after second-line chemotherapy.

Autologous stem cell transplantation (ASCT) was performed in five patients after second-line chemotherapy. Three of the 5 (8.9%) patients treated with ASCT achieved CR before transplantation. Two patients who achieved PR before transplantation died because of PD.

The 5-year OS and EFS were 85.8% and 89.6%, respectively (Figures 1a and 1b). The 5-year OS and EFS rates between patients treated with single chemotherapy or chemotherapy plus radiotherapy/surgery were not significantly different ($P > 0.05$). International prognostic index (IPI) ≥ 3, ECOG ≥ 2, high LDH levels, and stage at the time of diagnosis ≥ II2 significantly shortened 5-year OS and EFS ($P < 0.05$). The clinical variables and their prognostic impact on 5-year EFS and OS are shown in Table 2.

4. Discussion

We retrospectively analyzed the DLBC-PGL patients' clinical characteristics, survival rates, treatments, and prognostic factors affecting the survival rates.

Median age at the time of diagnosis and presenting symptoms were compatible with the literature (3,4,19). In this study, female predominance was documented, which was consistent with reports from Far East countries although literature from western countries reported male predominance (4,5,12,13,19–21).

In our study, the CR rate was 90.2% in patients at all stages, 94.3% at early stages, and 81.2% at late stages. In retrospective studies, the CR rate was 93%–100% in patients at all stages (12,14,15). In a prospective study comprising 45 early-stage DLBC-PGL patients treated with R-CHOP, CR was reported as 95% (11). In other retrospective studies that enrolled early-stage patients who were treated with R-CHOP, CR was between 87% and 100%, which is in agreement with our study (10,13,22). Tanaka et al. reported a CR rate of 78% in patients with late stages who were treated with R-CHOP[22]. Our results were comparable with those of previous studies.

There are contradicting data about the impact of rituximab on survival and response rates in patients with DLBC-PGL. Before the era of rituximab, CR was between 77.3% and 91% in patients at early stages and 76.6% at all stages (5,12,20,23). On the other hand, some studies demonstrated no significant difference in CR between patients treated with (92.5%–93.6%) or without (82.4%–93.9%) rituximab (14,15).

We found 5-year OS and EFS as 85.8% and 89.6%, respectively. In the literature, 5-year OS and EFS were 50%–93.3% and 81.6%–81.67%, respectively, before the era of rituximab (5,20,23). Aviles et al. reported 5-year OS of 95% and 5-year EFS of 95% in early-stage patients treated with R-CHOP. In that prospective study, when the data were compared to those of a historical control group, there was no statistically significant difference (11). No statistical significance in 3-year OS and DFS was demonstrated in patients treated with CHOP or R-CHOP chemotherapies in a study by Sohn et al. (14). In only one study on patients at all stages were 5-year OS (100% versus 63.3%) and DFS (100% versus 73.3%) lower in patients treated without rituximab (12). In a study by Kobayashi et al., 5-year OS of 100% was reported in early-stage patients treated with R-CHOP (13). In the light of these findings, there is a discrepancy about the impact of rituximab on OS and DFS in both early- and late-stage diseases.

Table 2. The clinical variables and their prognostic impact on five-year EFS and OS.

		OS%	P	EFS%	P
IPI score	0–2	92.6	0.004	93.3	0.006
	3–5	83.3		85.7	
B symptoms	Yes	60	0.033	71.8	0.04
	No	89.1		92.1	
Stage	I, II1	96.4	0.000	96.7	0.001
	≥II2	50.4		55.9	
LDH (U/L)	Normal	88.9	0.046	90	0.052
	>225	61.7		68.4	
ECOG performance status	≥2	25	0.000	25	0.001
	<2	87.3		90	
Age (years)	<60	86.1	0.597	87	0.651
	≥60	74		80.5	
Treatment modality	Single chemotherapy	83.5	0.207	85.9	0.119
	Chemotherapy+ radiotherapy/surgery	92.3		95.1	

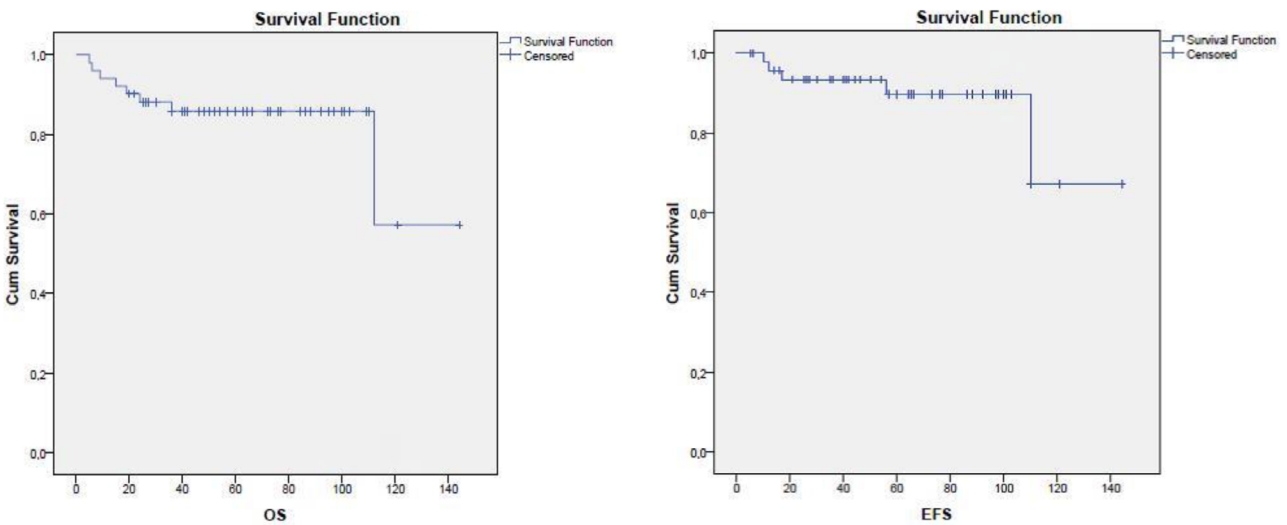

Figure 1. a) Kaplan–Meier curve for overall survival (85.8%) of 51 patients with primary gastric lymphoma; b) Kaplan–Meier curve for event-free survival (89.6%) of 51 patients with primary gastric lymphoma.

Similar to our results, OS and DFS/EFS have been reported to be adversely affected by late-stage disease, high β2 microglobulin and LDH levels, low albumin and hemoglobin levels, and poor performance status (14,20,22).

The indications for radiotherapy are not clear in the era of rituximab (3,4). Although radiotherapy in combination with R-CHOP was recommended in some studies, its effectiveness could not be proven in other studies (14,15,22–24). Some series suggested that conservative nonsurgical treatment achieves equal or better results than surgery (5,7,8,25). Therefore, surgery is only preferred in patients with complications like perforation and massive hemorrhage (3,4). In our study, there was no statistical difference in EFS or OS rate between single chemotherapy and chemotherapy plus radiotherapy/surgery. However, due to the relatively heterogeneous treatment and limited number of patients treated with surgery and/or radiotherapy, these therapies should be evaluated in large studies.

ASCT is the treatment of choice for patients in whom chemosensitivity to salvage treatment is still present. In

the PARMA trial, both EFS and OS were significantly superior in the transplantation group compared with the chemotherapy alone group (26). The CORAL study demonstrated that the response rate to salvage therapy was lower in patients previously treated with rituximab compared with rituximab-naive patients (83% vs 51%; $P < 0.001$) (27). In the rituximab era, there are no randomized data for treatment of relapse/refractory DLBC-PGL, but treatment as other relapsed/refractory DLBCL patients is recommended. Our limited data were compatible with the literature.

There are some constraints of our study. Firstly, it was a retrospective study with potential bias concerning patients and methods. Secondly, the number of patients was limited since it was a single institution experience and, thirdly, treatment modalities were varied. It might not be powerful enough to detect the significance of the benefit of single chemotherapy or chemotherapy plus surgery/radiotherapy. Fourthly, because of the low event count it was not possible to apply a Cox model and multivariate analysis to define the independent predictors of outcome variables.

Analysis of our center's data demonstrates that first line R-CHOP chemotherapy is as effective as R-CHOP plus radiotherapy/surgery in the treatment of DLBC-PGL patients. There was no statistical difference in EFS or OS rates between single chemotherapy and chemotherapy plus radiotherapy/surgery. Prospective, randomized, large cohort studies are needed to establish the optimal treatment for patients with DLBC-PGL.

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