Switching fractioned R-CHOP cycles to standard R-CHOP cycles guided by endoscopic ultrasonography in treating patients with primary gastric diffuse large B-cell lymphoma

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Abstract

Background: Primary gastric diffuse large B-cell lymphoma (PG-DLBCL) is a common subtype of extranodal non-Hodgkin lymphoma, with R-CHOP as the commonly used treatment regimen. However, full cycles of standard R-CHOP (Rituximab d1, 100% dose of CHOP d2) has the risk of severe bleeding or perforation, even leads to emergency surgery especially for those with deep lesions in their first 1-2 cycles of treatment. Full cycles of fractioned R-CHOP (Rituximab d1, 50% dose of CHOP d2 and d5) increases the safety of treatment but has the risk of resistance to the treatment. This study aims to explore the safety and efficacy of early fractioned R-CHOP cycles followed by standard R-CHOP cycles in patients with PG-DLBCL guided by endoscopic ultrasonography (EUS).

Methods: Thirty-one PG-DLBCL patients treated in Shanghai Cancer Center from October 2011 to October 2018 were analyzed in this retrospective study. All patients had lesions infiltrated to at least 3rd layer of stomach (5 layers totally) under EUS at baseline, and received EUS after every 2 cycles’ treatment. Patients switched to standard R-CHOP if they showed the reduced infiltrated layers and restricted lesions after fractioned R-CHOP cycles. Fecal occult blood test and enhanced abdominal CT scan were also referred.

Results: 77.4% (24/31) patients successfully switched after two treatment cycles. The ORR, 5-year PFS and OS were 93.5%, 75% and 84%, respectively. No treatment delay or dosage reduction from gastric adverse event was observed. More importantly, none of patients in our study suffered from severe bleeding or perforation during the treatment. Kaplan-Meier analysis showed that PG-DLBCL patients characterized multiple localization (sites >1), large size (≥3cm), having B symptoms, lower serum albumin (ALB) level (≤ 35g/L), and elevated LDH level (>250U/L) associated with worse PFS and OS.

Conclusions: Our data indicate that it might be an effective approach in treating deeply infiltrated PG-DLBCL patients by switching fractioned R-CHOP cycles to standard R-CHOP
cycles guided by EUS. Further prospective study about the approach is needed to confirm the conclusion.

**Background**

Primary gastric diffuse large B-cell lymphoma (PG-DLBCL) is one of the most common extranodal non-Hodgkin lymphomas (NHLs) [1]. Treatment of the disease includes surgery, chemotherapy, and radiotherapy alone or combined with each other. And the best regimen has not been standardized. The general consensus is that treatment should be taken concerning the principal clinical issues of patients, and biological behavior of the malignances, which guide the doctors to make proper options whether to take local-therapy or systemic chemotherapy [2–4]. 6–8 cycles of R-CHOP are usually used to treat the disease. However, full cycles of standard R-CHOP (Rituximab d1, 100% dose of CHOP d2) have the risk of severe bleeding or perforation, even leading to emergency surgery especially for those with deep lesions in their first 1–2 cycles of treatment. However, full cycles of fractioned R-CHOP (Rituximab d1, 50% dose of CHOP d2 and d5) increase the safety of treatment but have the risk of resistance to the treatment.

Gastric endoscopic ultrasound (EUS) has emerged as one of the best tools for locoregional staging in PGL, it also has predictive value in diagnosis, evaluating treatment response and post-treatment follow-up [5, 6]. It could visualize 5-layer structure of stomach, and could provide important information on prognostic features of PG-DLBCL and may contribute to the determination of the therapeutic approach.

In the current study, we retrospectively reviewed a cohort of primary gastric diffuse large B-cell lymphoma patients to provide insights into the safety and efficacy of early fractioned R-CHOP cycles followed by standard R-CHOP cycles in primary gastric DLBCL guided by endoscopic ultrasonography (EUS).
Materials And Methods

Patients

Thirty-one PG-DLBCL patients treated in Shanghai Cancer Center, China from October 2011 to October 2018 were analyzed in this retrospective study. All patients were pathologically confirmed as DLBCL through biopsy samples, and all pathological results were reviewed by experienced pathologists in pathology department of Shanghai Cancer Center. Patients enrolled in our study were all from Asian, and ECOG were 1-2. This study was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center. Survival data were available with a median follow-up of 513 days (range 105~2,607 days). The demographic details, clinico-pathologic characteristics of the patients are summarized in Table 1.

Treatment modalities of PG-DLBCL patients

All patients had EUS examination before treatment, and had lesions infiltrated to at least the 3rd layer of stomach (5 layers totally) at baseline. Patients received EUS after every 2 cycles of treatment, and PET-CT was required at the end of treatment. Response criteria were adapted from the international consensus reported by Cheson et al. Toxicities during treatment were evaluated according to the National Cancer Institute common toxicity criteria scale (version 4.0).

None of patients in our study underwent surgery at the onset of disease. All the 31 patients received initial fractioned R-CHOP (Rituximab d1, 50% dose of CHOP d2 and d5) for at least 2 cycles. Patients switched to standard R-CHOP if they showed the reduced infiltrated layers and restricted lesions under EUS after fractioned R-CHOP cycles. Fecal occult blood test and enhanced abdominal CT scan were also referred.

Statistical analysis

All analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago). Kaplan-Meier
survival curves were constructed for survival analyses, and differences were tested by the log-rank test. Overall survival was defined as the time between the date of diagnosis and the date of death or the date of last contact. Progression-free survival (PFS) refers to the period from the diagnosis to the observed progression of the disease or the occurrence of death for any reason. The data of patients alive at the end of the study were censored. All $P$ values were two-sided, and the results were considered significant if $P < 0.05$.

Results

Patient characteristics

All 31 cases enrolled in this study were from hospitalized patients, of whom 15 (48.4%) were men and 16 (51.6%) were women. The median age was 54 years (range 18 to 80 years). According to the 1994 Lugano modifications of the Musshoff staging classification [7], 21 patients (67.8%) were diagnosed with stage I and II disease, 1 (3.2%) and 9 (29.0%) patients were diagnosed with stage IIE and IV disease, respectively. Symptoms of the patients with this disease were unspecific. The most common were abdominal pain or discomfort, gastric hemorrhage, lack of appetite and weight loss. All patients received EUS and PET before treatment. Basic features of the patients are recorded concerning the clinical/pathological parameters of tumors (Table 1). We found that 13 (41.9%) patients had lesions more than one site of stomach. And the most frequent site of PG-DLBCLs in our study was antrum and the body of the stomach (Table 2).

Treatment effect of the patients

Overall response rate of the patients was 93.5% (29/31). No treatment delay or dosage reduction from gastric adverse event was observed. More importantly, no patients in our study suffered from severe bleeding or perforation during the treatment. 5-year progression free survival rate and 5-year overall survival rate were 75% and 84%, respectively. 3 (9.7%) patients died of the disease at the date of last follow-up. OS and
PFS of all patients in our study were showed in Fig 1.

**Effect of clinicopathological parameters on PFS and OS of PG-DLBCL patients**

Kaplan-Meier analysis showed that PG-DLBCL patients characterized by late stage (stage IV) \( (P = 0.025) \), multiple localization (sites >1) \( (P = 0.049) \), large size \( (P = 0.004) \), higher IPI \( (P = 0.048) \), having B symptoms \( (P < 0.001) \), lower serum albumin (ALB) level \( (P < 0.001) \), and elevated LDH level \( (P = 0.045) \) had shorter PFS (Figure 2). And patients with multiple localization \( (P = 0.032) \), large size \( (\geq 3cm) \) \( (P = 0.044) \), and deep lesions \( (\geq 11mm) \) \( (P = 0.031) \) under EUS, having B symptoms \( (P < 0.001) \), lower ALB level \( (\leq 35g/L) \) \( (P < 0.001) \), and elevated LDH level \( (> 250U/L) \) \( (P = 0.012) \) associated with worse OS (Figure 3).

**Discussion**

DLBCL is a common subtype of primary gastric lymphoma. Primary gastric diffuse large B-cell lymphoma (PG-DLBCL) has been treated with various modalities, such as surgery, chemotherapy and radiotherapy alone or in combination with each other. Combining rituximab with doxorubicin, vincristine and prednisone (R-CHOP) is considered to be the standard regimen to treat the disease \([8-11]\). In our study, we evaluated the feasibility and efficacy of switching fractioned R-CHOP to standard R-CHOP in the treatment of PG-DLBCL patients.

Traditionally, radical gastrectomy was regarded as the front-line treatment for PGL. In recent years, surgery is relegated only to patients with massive bleeding or perforation at presentation \([4]\). Besides, surgery could lower the quality of life and postpone the beginning of chemotherapy. All patients enrolled in our study had high possibility of perforation and bleeding during treatment. However, after applying the initial treatment of fractioned R-CHOP, no adverse effects such as bleeding or perforation were observed in patients included in this study.

Endoscopic ultrasound (EUS) is a valuable tool in the diagnosis of PGL patients, as it could
diagnose and utilize the loco-regional staging of the disease. Furthermore, EUS could measure invasive depth of lesions that could not be accomplished by ordinary gastroscopy. Our previous work provided new insights about evaluation of PG-DLBCLs based on EUS results. That large (≥ 3 cm), or deep lesions (≥ 11 mm) were significantly correlated with the inferior OS of PG-DLBCL patients [12]. This study further extends its role in the guidance of treatment when to switch to standard R-CHOP regimens.

In our previous work, we illustrated some prognostic factors of PG-DLBCL patients. In the present study, we also confirmed that tumor located at multiple sites of stomach, having B symptoms, lower ALB levels, elevated LDH level could act as adverse prognostic biomarkers. Besides, the tumoral size and depth examined by endoscopic methodology were valuable parameters to predict the outcome of PG-DLBCL patients.

PG-DLBCL lesions with large size and deep depth under EUS had the great risk of bleeding or perforation during treatment, and often suffered worse PFS and OS. Full cycles of standard R-CHOP (Rituximab d1, 100% dose of CHOP d2) had the risk of severe bleeding or perforation, even leading to emergency surgery especially for those with large and deep lesions in their first 1–2 cycles of treatment. Full cycles of fractioned R-CHOP (Rituximab d1, 50% dose of CHOP d2 and d5) increase the safety but might cause resistance to the treatment. Switching fractioned R-CHOP to standard R-CHOP could get the great balance between treatment effects and avoiding sever side effects. Besides, our work might shed light on further investigations of exploring other treatment regimens such as combining with other new agent, such as lenalidomide, ibrutinib, polatuzumab vedotin, etc., or receiving ASCT after first line treatment [13-16], in order to develop an optimal standard in clinical management of this disease.

Conclusions

Our data indicate that it might be an effective approach in treating deeply infiltrated PG-
DLBCL patients by switching fractioned R-CHOP cycles to standard R-CHOP cycles guided by EUS.

Abbreviations
DLBCL
diffuse large B-cell lymphoma
PG-DLBCL
primary gastric diffuse large B-cell lymphoma
EUS
endoscopic ultrasonography
NHL
non-Hodgkin lymphoma
R-CHOP
rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
ORR
overall response rate
PFS
progression-free survival
OS
overall survival

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center. All patients signed informed consent forms for participate into the study.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable.
**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

YZL analyzed and interpreted the patients data, and have drafted the work. YML analyzed parameters under endoscopic ultrasonography and performed the follow-up work. QLZ, XJL and FFL have made substantial contributions to acquisition data. XNH, and JNC supervised the work. PZ and KX substantively revised the manuscript. All authors read and approved the final manuscript.

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**References**

1. Koch P, Probst A, Berdel WE, Willich NA, Reinartz G, Brockmann J, et al. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 23: 7050-9.

2. Mehmet K, Sener C, Uyeturk U, Seker M, Tastekin D, Tonyali O, et al. Treatment modalities in primary gastric lymphoma: the effect of rituximab and surgical treatment. A study by the Anatolian Society of Medical Oncology. Contemporary oncology. 2014; 18: 273-8.

3. Huang HW, Jiang YB, Fu TW, Xu T, Chen XC, Jin ZM, et al. [Efficacy of surgery and rituximab in primary gastric diffuse large B-cell lymphoma]. Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi. 2016; 37: 602-6.
4. Ikoma N, Badgwell BD, Mansfield PF. Multimodality Treatment of Gastric Lymphoma. The Surgical clinics of North America. 2017; 97: 405-20.

5. Vanis N, Mesihovic R, Ibricevic L, Dobrila-Dintinjana R. Predictive value of endoscopic ultrasound in diagnosis and staging of primary gastric lymphoma. Collegium antropologicum. 2013; 37 Suppl 1: 291-7.

6. Vetro C, Chiarenza A, Romano A, Amico I, Calafiore V, Di Raimondo C, et al. Prognostic assessment and treatment of primary gastric lymphomas: how endoscopic ultrasonography can help in tailoring patient management. Clinical lymphoma, myeloma & leukemia. 2014; 14: 179-85.

7. Rohatiner A, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology. 1994; 5: 397-400.

8. Coiffier B. State-of-the-art therapeutics: diffuse large B-cell lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 23: 6387-93.

9. Zhang HY, Guan ZZ, Wang B, Huang HQ, Xia ZJ, Lin TY. [Relationship between clinopathological features and outcome of rituximab treatment for diffuse large B-cell lymphoma]. Zhonghua zhong liu za zhi [Chinese journal of oncology]. 2008; 30: 381-4.

10. Zhang J, Li G, Yang H, Liu X, Cao J. Rituximab in treatment of primary gastric diffuse large B-cell lymphoma. Leukemia & lymphoma. 2012; 53: 2175-81.

11. Zhao W, Gao Y, Bai B, Cai QC, Wang XX, Cai QQ, et al. Safety and efficacy of non-initial rapid infusion of rituximab plus chemotherapy in Chinese patients with CD20+ non-Hodgkin's lymphoma. Expert opinion on drug safety. 2015; 14: 21-9.
12. Liu YZ, Xue K, Wang BS, Li CY, Lv FF, Jin J, et al. The size and depth of lesions measured by endoscopic ultrasonography are novel prognostic factors of primary gastric diffuse large B-cell lymphoma. Leukemia & lymphoma. 2019; 60: 934-9.

13. Chamuleau MED, Burggraaff CN, Nijland M, Bakunina K, Mous R, Lugtenburg PJ, et al. Treatment of patients with MYC rearrangement positive large B-cell lymphoma with R-CHOP plus lenalidomide: results of a multicenter HOVON phase II trial. Haematologica. 2019.

14. Denker S, Bittner A, Na IK, Kase J, Frick M, Anagnostopoulos I, et al. A Phase I/II first-line study of R-CHOP plus B-cell receptor/NF-kappaB-double-targeting to molecularly assess therapy response. International journal of hematologic oncology. 2019; 8: IJH20.

15. Polatuzumab Vedotin Approved for DLBCL. Cancer discovery. 2019; 9: OF2.

16. Zhao Y, Wang H, Jin S, Zheng J, Huang M, Tang Y, et al. Prognostic analysis of DLBCL patients and the role of upfront ASCT in high-intermediate and high-risk patients. Oncotarget. 2017; 8: 73168-76.

Tables

Table 1. Baseline characteristics of 31 PG-DLBCL patients
| Characteristic         | PG-DLBCL | %  |
|-----------------------|----------|----|
| **Gender**            |          |    |
| Male                  | 15       | 48.4 |
| Female                | 16       | 51.6 |
| **Age at diagnosis**  |          |    |
| >60                   | 15       | 48.4 |
| ≤60                   | 16       | 51.6 |
| **Lugano stage**      |          |    |
| I                     | 4        | 12.9 |
| II 1                  | 6        | 19.4 |
| II 2                  | 11       | 35.5 |
| II E                  | 1        | 3.2  |
| IV                    | 9        | 29.0 |
| **Subtypes (n=28)**   |          |    |
| GCB                   | 14       | 50.0 |
| Non-GCB               | 14       | 50.0 |
| **B symptoms**        |          |    |
| Yes                   | 5        | 16.1 |
| No                    | 26       | 83.9 |
| **IPI score**         |          |    |
| 0-1                   | 21       | 67.7 |
| ≥ 2                   | 10       | 32.3 |
| **ALB**               |          |    |
| ≤35                   | 3        | 9.7  |
| >35                   | 28       | 90.3 |
| **LDH**               |          |    |
| Normal(≤250)          | 25       | 80.6 |
| Elevated              | 6        | 19.4 |
| **HBSAg positive**    |          |    |
| Yes                   | 5        | 16.1 |
| No                    | 26       | 83.9 |
| **Family history**    |          |    |
| Yes                   | 4        | 12.9 |
| No                    | 27       | 87.1 |
| **SUVmax before treatment** | |    |
| Mean±SD               | 17.92±10.49 |    |

ALB = albumin; LDH = lactic dehydrogenase

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone

R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
Table 2. Features of the lesion in PG-DLBCL patients receiving EUS before treatment*

| Characteristics                              | Case number | Proportion (%) |
|----------------------------------------------|-------------|----------------|
| **Site**                                     |             |                |
| Body                                         | 10          | 32.3           |
| Antrum                                       | 8           | 25.8           |
| Multiple locations                           | 2 13        | 41.9           |
| **Size**                                     |             |                |
| <3cm                                         | 18          | 58.1           |
| ≥3cm                                         | 13          | 41.9           |
| **Depth (n=30)**                              |             |                |
| <11mm                                        | 18          | 60.0           |
| ≥11mm                                        | 12          | 40.0           |
| **Depth of infiltration (n=30)**              |             |                |
| Submucosa                                    | 2           | 6.6            |
| Muscular                                     | 17          | 56.7           |
| Serosa                                       | 11          | 36.7           |

Figures
Progression-free survival (PFS) and overall survival (OS) of PG-DLBCL patients in our study. Kaplan-Meier curves showing the PFS (A) and OS (B) of PG-DLBCL patients in our study.
Figure 2

Correlation of clinical and laboratory parameters on progression free survival (PFS) of PG-DLBCL patients Kaplan-Meier curves showing the association between stage (A), location (B), size (C), IPI (D), B symptoms (E), serum ALB level (F), LDH level (G) and PFS of PG-DLBCL patients in our study. All the P values are shown in the graph, by log-rank test.
Association of clinical and laboratory parameters on overall survival (OS) of PG-DLBCL patients Kaplan-Meier curves showing the association between location (A), size (B), depth under EUS (C), B symptoms (D), serum ALB level (E), LDH level (F) and OS of PG-DLBCL patients in our study. All the P values are shown in the graph, by log-rank test.