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Original Article

Molecular phenotypes and treatment modalities in predicting the prognosis for patients with gastrointestinal diffuse large B-cell lymphoma

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Abstract: The prognosis of patients with gastrointestinal diffuse large B-cell lymphoma (GI-DLBCL) varies remarkably. This study aims to evaluate the role of molecular phenotypes and treatment modalities in predicting the prognosis for patients with GI-DLBCL. From March 2006 to January 2016, ninety-nine patients with newly diagnosed GI-DLBCL were enrolled in this retrospective study. Patients treated with surgery followed by chemotherapy (SCT, 48 cases) had a significant greater 2-year progression free survival (PFS, 79.4% vs. 63.6%, $P = 0.040$) and overall survival (OS, 94.7% vs. 85.0%, $P = 0.039$) than those treated with chemotherapy alone (CTa, 51 cases). No significant differences of 2-year PFS (68.8% vs. 73.2%, $P = 0.639$) and OS (93.9% vs. 85.6%, $P = 0.150$) were observed between germinal center B-cell-like (GCB, 41 cases) and non-GCB (40 cases) phenotypes. In the GCB group, patients treated with SCT (25 cases) had a significantly higher 2-year PFS (83.1% vs. 49.2%, $P = 0.018$) than those treated with CTa (16 cases), but not in the 2-year OS ($P = 0.095$). In the non-GCB group, no significant difference of survival was observed between these two treatment modalities ($P > 0.05$). In multivariate analysis, treatment modality was not an independent prognostic factor in either the whole cases or the GCB group (both $P > 0.05$). Molecular phenotypes of GCB and non-GCB might be failed to predict the survival for patients with GI-DLBCL. Patients treated with SCT had a higher survival in the whole cases and in the GCB group, but it was not an independent prognostic index. Multi-factors should be evaluated to select treatment modality.

Keywords: Gastrointestinal, diffuse large B-cell lymphoma, molecular phenotypes, surgery, chemotherapy

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most frequent histological subtype of non-Hodgkin lymphoma [1], is a heterogeneous entities with clinical presentation, pathological classification and genetic characteristic [2]. Three distinct subtypes of DLBCL, germinal-center B-cell-like (GCB), activated B-cell-like (ABC), and a "third type", were identified by Alizadeh et al. [3] in 2000. Four years later, Hans et al. [4] reported that the phenotypes of DLBCL could be divided into GCB and non-GCB phenotypes by determining the expression of CD10, BCL6, and MUM1 with immunohistochemistry. Moreover, the survival of patients with GCB phenotype was better than those with non-GCB. However, the prognostic impact of the molecular phenotypes between GCB and non-GCB has not well been confirmed in all studies [5, 6].

Gastrointestinal DLBCL (GI-DLBCL) is the predominant pathological subtype and accounts for approximately 45-59% of all gastrointestinal lymphomas [7, 8]. But the optimal treatment strategy has not well been established, mainly due to the small sample size, various histological subtypes [9], and many risk factors [10]. Previous studies have shown that two major therapeutic modalities, surgery followed by chemotherapy (SCT) and chemotherapy alone (CTa) [11, 12], were used for patients with GI-DLBCL. However, the results between these two strategies were still under controversial in recent studies. Lee et al. [13] demonstrated that

Table 1. Baseline characteristics of the ninety-nine patients with gastrointestinal diffuse large B-cell lymphoma

Characteristics	No. of patients (%)	2-year PFS (%)	χ^2 value	*P* value	2-year OS (%)	χ^2 value	*P* value
Sex			0.615	0.433		0.016	0.900
Male	66 (66.7)	68.4			88.2		
Female	33 (33.3)	76.6			92.3		
Lugano stage			11.29	0.001		9.661	0.004
I-II1	57 (57.6)	89.0			97.5		
II2, IIE, IV	42 (42.4)	55.3			82.3		
Age			4.267	0.039		4.418	0.036
≤ 60	79 (79.8)	77.3			93.1		
> 60	20 (20.2)	45.7			76.5		
ECOG PS			29.54	0.001		24.22	0.001
< 2	87 (87.9)	78.8			93.1		
≥ 2	12 (12.1)	16.7			66.7		
LDH concentration			16.91	0.001		8.387	0.004
≤ ULN	71 (71.7)	81.2			96.3		
> ULN	28 (28.3)	46.4			73.3		
No.of extra-nodal sites			2.901	0.089		2.67	0.102
< 2	72 (72.7)	77			91.5		
≥ 2	27 (27.3)	57.9			85.1		
IPI score			14.54	0.001		7.237	0.007
0-2	73 (73.7)	82.6			95		
3-5	26 (26.3)	42.3			75.3		
Molecular phenotypes			0.220	0.639		2.073	0.150
GCB	41 (50.6)	68.8			93.9		
non-GCB	40 (49.4)	73.2			85.6		
Treatment modality			4.232	0.040		4.26	0.039
CTa	51 (51.5)	63.6			85.0		
SCT	48 (48.5)	79.4			94.7		

Note: *P*-value was calculated by log–rank test; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; IPI, international prognostic index; GCB, germinal-center B-cell-like; non-GCB, non-germinal-center B-cell-like; CTa, chemotherapy alone; SCT, surgery followed by chemotherapy; PFS, progression-free survival; OS, overall survival.

patients with intestinal DLBCL treated with surgery followed by rituximab in combination with cyclophosphamide, adriamycin, vincristine, and prednisolone (R-CHOP) had a better survival rate than those treated with R-CHOP alone. But Li et al. [14] indicated that the treatment of SCT could not improve the overall survival for patients with GI-DLBCL.

Considering the conflicting results of the treatment modalities and molecular phenotypes, hence, in this study, the relationship between molecular phenotypes, treatment modalities and the prognosis of patients with gastrointestinal diffuse large B-cell lymphoma (GI-DLBCL) was evaluated.

Materials and methods

Patient selection

From Mar 2006 through Jan 2016, a total of 99 consecutive patients with newly diagnosed GI-DLBCL were reviewed in the retrospective study. The patients' clinical and pathological features were summarized in **Table 1**. Inclusion criteria were as follows: (i) with histological proven DLBCL; (ii) treated with surgery followed by rituximab combined with cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) or R-CHOP alone; and (iii) the phenotypes of GCB and non-GCB were obtained in some cases. Patients were excluded: (i) if exhib-

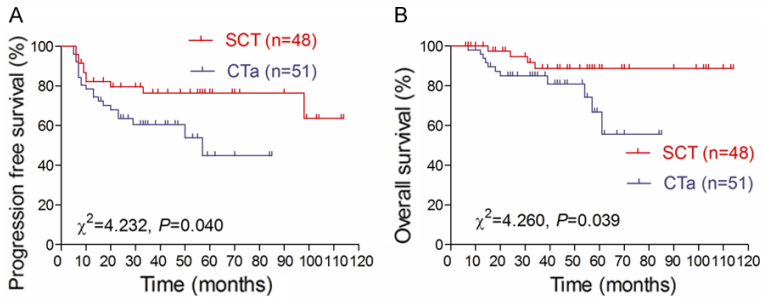

Figure 1. PFS (A) and OS (B) according to the treatment modalities between surgery followed by chemotherapy (SCT) and chemotherapy alone (CTa) in 99 patients with gastrointestinal diffuse large B-cell lymphoma.

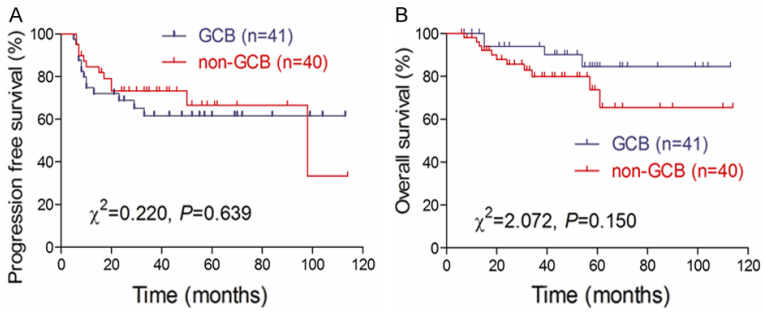

Figure 2. PFS (A) and OS (B) according to the molecular phenotypes between the molecular phenotypes of germinal center B-cell-like (GCB) and non- germinal center B-cell-like (non-GCB) in 81 patients with gastrointestinal diffuse large B-cell lymphoma.

ited evidence of a secondary malignant tumor; (ii) the patient treatment notes were unavailable; or (iii) there was no tissue available.

This study was approved by the Ethics Committee of Nanfang hospital, Southern medical university, China. Informed consent was waived because the nature of this retrospective study.

Clinical and pathological features

Pathological diagnosis of DLBCL was performed according the World Health Organization (WHO) criteria [15]. All patients with GI-DLBCL were diagnosed according to the definition proposed in previous reports [16, 17]. The clinical stage was classified according to the Lugano staging system which was specified for gastrointestinal lymphomas [18]. International prognostic index (IPI) was used to allocate patients to low and low intermediate risk groups, and high intermediate and high risk groups [19]. The clinical features of age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), Lugano stage, serum lactate dehydrogenase (LDH) level and extra-nodal involvements were obtained at the time of diagnosis. All tissue biopsies were obtained by endoscopic biopsy or surgery and stained with hematoxylin and eosin. The phenotypes of GCB and non-GCB were discriminated by Hans' criteria [4].

Treatment strategy

Two groups were obtained from the treatment modalities: surgery followed by chemotherapy (SCT) and chemotherapy alone (CTa). With the exception of urgent surgery, such as obstruction, bleeding, or perforation, the treatment modalities were decided by investigators at Nanfang hospital. As for surgery, complete surgical resection of the gastrointestinal tumor and regional lymph nodes were performed. The chemotherapy included 6-8 cycles of R-CHOP regimens at standard doses (rituximab 375 mg/m^2 intravenously on day 0; cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 but not more than 2.0 mg, and doxorubicin 50 mg/m^2 each administered intravenously on day 1; and prednisone 100 mg daily, given orally on days 1 to 5) and then every 3 weeks a cycle.

Response evaluation

Combined with the examination results of patients before and after treatment, such as computed tomography, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission computed tomography (PET)/computed tomography, the progression or recurrence of the disease was determined by the International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017) [20]. Complete response (CR) was defined as complete disappearance of all target lesions and all nodes with long axis < 10 mm, or > 30% decrease in the sum of longest diameters of target lesions (PR) with normalization of ^{18}F-FDG-PET. Partial response (PR) was designated as > 30% decrease in the sum of

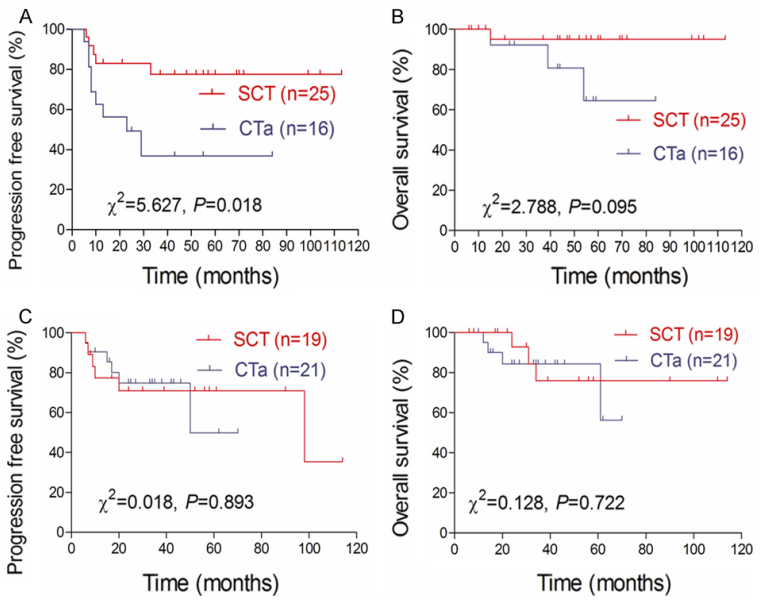

Figure 3. PFS and OS according to the treatment modalities and molecular phenotypes. A and B. Showed the differences of PFS and OS between surgery followed by chemotherapy (SCT) and chemotherapy alone (CTa) in the germinal center B-cell-like (GCB) group. C and D. Showed the differences of PFS and OS between SCT and CTa in the non-GCB group.

longest diameters of target lesions but not a CR. Stable disease (SD) was defined as < 10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions. Progressive disease (PD) was defined as > 20% increase in the sum of longest diameters of target lesions, or for small lymph nodes measuring < 15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm, or appearance of a new lesion.

Statistical analysis

SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA) were used for statistical analyses. Descriptive statistics of clinical characteristics were generated as proportions. End points were progression free survival rate (PFS; defined as time from diagnosis to progression, relapse, or death from any cause) and overall survival rate (OS; defined as time from diagnosis to death from any cause). PFS and OS were determined by Kaplan-Meier analysis and the differences across groups were analyzed by log-rank test. Prognostic factors were tested by univariate and multivariate Cox proportional hazard models. All tests were considered significance at the two-sided 0.05 significant level.

Results

Patient characteristics

In total, 99 patients were enrolled in this retrospective study. The clinical and pathological characteristics and outcomes were summarized in **Table 1**. The median age was 48.5 years (range, 11 to 82 years), and the male to female ratio was 2:1. The median follow-up duration was 25 months (range, 5 to 114 months). The distribution of patients into stages I, II1, II2, IIE and IV was 28.3% (28/99), 19.2% (19/99), 10.1% (10/99), 20.2% (20/99) and 22.2% (22/99), respectively. The ECOG performance status was good in most of the enrolled patients (score 0-1; 87.9%). There were 48 patients treated with SCT and 51 patients treated with CTa, and 41 patients with GCB phenotype and 40 patients with non-GCB phenotype.

Outcomes according to treatment modalities

In the whole cases, the 2-year PFS and OS were 70.9% (95% CI 60.4%-79.1%) and 89.5% (95% CI 80.8%-94.5%), respectively. Patients treated with SCT had a significant greater 2-year PFS (79.4% vs. 63.6%, χ^2 = 4.232, P = 0.040) and OS (94.7% vs. 85.0%, χ^2 = 4.260, P = 0.039) than those treated with CTa (**Figure 1**).

Outcomes according to molecular phenotypes

Of the 41 patients with GCB phenotype, the 2-year PFS and OS were 68.8% and 93.9%, respectively. In the non-GCB group (40 cases), the 2-year PFS and OS were 73.2% and 85.6%, respectively. No significant differences of the 2-year PFS and OS were observed between these two groups (χ^2 = 0.220, P = 0.639 and χ^2 = 2.072, P = 0.150, **Figure 2**).

Outcomes according to treatment modalities and molecular phenotypes

In the GCB group, 25 patients treated with SCT, the 2-year PFS was higher than those (16

Table 2. Baseline characteristics of the forty-one patients with GCB phenotype of diffuse large B-cell lymphoma

Characteristics	No. of patients	2-year PFS (%)	χ^2 value	*P* value	2-year OS (%)	χ^2 value	*P* value
Sex			2.643	0.104		0.915	0.339
Male	30 (73.2)	62.6			92.6		
Female	11 (26.8)	90.9			100		
Lugano stage			7.801	0.005		4.202	0.040
I-II1	20 (48.8)	95.0			100		
II2, IIE, IV	21 (51.2)	44.4			88.2		
Age			8.313	0.004		3.399	0.065
≤ 60	34 (82.9)	78.6			96.4		
> 60	7 (17.1)	17.9			80		
ECOG PS			19.92	0.001		12.96	0.001
< 2	36 (87.8)	79.1			96.4		
≥ 2	5 (12.2)	0.00			80.0		
LDH concentration			11.54	0.001		3.041	0.081
≤ ULN	28 (68.3)	83.3			100		
> ULN	13 (31.7)	38.5			81.8		
No. of extra-nodal sites			2.634	0.105		0.737	0.391
< 2	27 (65.9)	80.4			95.5		
≥ 2	14 (34.1)	49.0			90.9		
IPI score			13.92	0.001		4.635	0.031
0-2	29 (70.7)	89.3			100		
3-5	12 (29.3)	25.0			80.0		
Treatment modality			5.627	0.018		2.788	0.095
CTa	16 (39.0)	49.2			92.3		
SCT	25 (61.0)	83.1			95.0		

Table 3. Multivariate Cox regression analysis of progression free survival for the whole cases

Characteristics	HR	95.0% CI for HR	*P* value
Age (≤ 60 vs. > 60 y)	2.059	0.919-4.651	0.079
Lugano stage (I-II1 vs. II2-IV)	2.314	0.796-6.724	0.123
ECOG PS (< 2 vs. ≥ 2)	5.090	1.768-14.651	0.003
LDH (> ULN vs. ≤ ULN)	4.034	1.567-10.385	0.004
IPI score (0-2 vs. 3-5)	0.467	0.144-1.512	0.204
Treatment modality (SCT vs. CTa)	0.889	0.357-2.216	0.801

patients) treated with CTa (83.1% vs. 49.2%, χ^2 = 5.627, *P* = 0.018, **Figure 3A**), but not in the 2-year OS (95.0% vs. 92.3%, χ^2 = 2.788, *P* = 0.095, **Figure 3B**). In the non-GCB group, 19 patients treated with SCT, and no significant differences of the 2-year PFS and OS were observed when compared with those (21 patients) treated with CTa (χ^2 = 0.018, *P* = 0.893 and χ^2 = 0.128, *P* = 0.722, **Figure 3C**, **3D**).

In the group of patients treated with CTa, the 2-year PFS and OS revealed no significant differences between the phenotypes of GCB (16 patients) and non-GCB (21 patients) (χ^2 = 3.142, *P* = 0.076 and χ^2 = 0.008, *P* = 0.930). In the group of patients treated with SCT, 25 patients with GCB phenotypes and 19 patients with non-GCB phenotypes, and no significant differences of the 2-year PFS and OS were observed between these two phenotypes (χ^2 = 0.777, *P* = 0.378 and χ^2 = 1.946, *P* = 0.163).

Univariate and multivariate analysis of the related prognostic factors

In whole cases, univariate analysis indicated that the following five clinical factors, such as IPI score, Lugano stage, ECOG PS, LDH level and age, and treatment modality could be used

Table 4. Multivariate Cox regression analysis of overall survival for the whole cases

Characteristic	HR	95.0% CI for HR	*P* value
Age (≤ 60 vs. > 60 y)	2.883	0.908-9.154	0.072
Lugano stage (I-II1 vs. II2-IV)	5.157	0.915-29.072	0.063
ECOG PS (< 2 vs. ≥ 2)	5.982	1.515-23.618	0.011
LDH (> ULN vs. ≤ ULN)	3.459	0.867-13.798	0.079
IPI score (0-2 vs. 3-5)	0.257	0.047-1.400	0.116
Treatment modality (SCT vs. CTa)	1.235	0.300-5.079	0.770

Table 5. Multivariate Cox regression analysis of progression free survival for patients with GCB phenotype

Characteristic	HR	95.0% CI for HR	*P* value
Age (≤ 60 vs. > 60 y)	4.277	1.160-15.768	0.029
Lugano stage (I-II1 vs. II2-IV)	1.254	0.150-10.493	0.835
ECOG PS (< 2 vs. ≥ 2)	7.450	1.380-40.218	0.020
LDH (> ULN vs. ≤ ULN)	3.679	0.874-15.484	0.076
IPI score (0-2 vs. 3-5)	0.908	0.147-5.616	0.917
Treatment modality (SCT vs. CTa)	1.506	0.307-7.383	0.614

to predict the 2-year PFS and OS in the whole cases (**Table 1**). Those factors that correlated with a significantly survival were carried out in the multivariate analysis. Multivariate analysis indicated that treatment modality was not an independent factor to predict the PFS (**Table 3**) and OS (**Table 4**).

In the GCB group, univariate analysis showed that age, Lugano stage, ECOG PS, LDH level, IPI score and treatment modality could be used to predict the 2-year PFS (**Table 2**). Multivariate analysis (**Table 4**) indicated that treatment modality was not an independent factor to predict the PFS (**Table 5**).

Discussion

In the present study, prognosis of patients with GI-DLBCL by combining molecular phenotypes and treatment modalities was evaluated. The results show that the phenotypes of GCB and non-GCB might be failed to predict the survival for patients with GI-DLBCL. Patients treated with surgery followed by chemotherapy (SCT) seemed to have a longer survival than those treated with chemotherapy alone (CTa) in the whole cases and in the GCB phenotype, but it was not an independent prognostic factor. Multi-factors should be evaluated to select treatment modality.

The phenotypes of GCB and non-GCB have been identified by Hans et al. [4]. The outcome of DLBCL patients with GCB phenotype had a better survival rate than those with non-GCB phenotype. But later, several studies showed that rituximab in combination with CHOP seemed to eliminate the prognostic value of GCB and non-GCB phenotypes in DLBCL patients [5, 21]. As for GI-DLBCL, one of the most frequent site and subtype of extra-nodal lymphoma, however, little information was available about the survival difference between the phenotypes of GCB and non-GCB. In our results, no significant difference of outcome was observed between these two phenotypes, no matter which treatment modality was used. Therefore, phenotypes of GCB and non-GCB might fail to predict survival for patients with GI-DLBCL in the rituximab era.

In addition, the treatment modality of GI-DLBCL has not well been established to date. The result of SCT and CTa remains under controversial in many studies. Kim et al. [11] demonstrated that patients with intestinal DLBCL who received SCT had a higher survival rate than those treated with CTa. In another report by Aviles et al. [22] who indicated a parallel results, but it's for patients with primary gastric DLBLC. However, in another published article, the treatment strategy of SCT for intestinal DLBCL was not an independent prognostic factor even though the patients had a higher survival rate than those treated with CTa [13]. Further, Li et al. [14] showed an opposite result that SCT could not improve the overall survival for patients with GI-DLBCL. Multiple causes may lead to these conflicting results, such as the small sample size, the different study sites, various prognostic factors and so on. However, all of these studies didn't combine the molecular phenotypes and treatment modalities to evaluate the prognosis for patients with GI-DLBCL. Therefore, in this study, patients with GCB phenotype had a higher PFS than those with non-GCB phenotype when treated with SCT. But in multivariate analysis, the treatment modality was not an independent factor to predict the survival for patients with GI-DLBCL, either in the whole cases or in the GCB group.

IPI is an important prognostic tool for patients with DLBCL [19, 23]. Five risk factors were included, such as age, ECOG PS, LDH level, Ann Arbor stage and involvement of extra-nodal sites. Previous studies have reported that intestinal DLBCL patients with stage III-IV had a lower survival rate than those with stage I-II [14, 24]. Moreover, patients with LDH level > upper limit of normal (ULN) and ECOG PS ≥ 2 also indicated a worse outcome [14]. However, the capacity of IPI to predict the survival has declined in recent reports, especially for the high and high-intermediate risk groups [25, 26]. Here, univariate analysis indicated that the clinical features of age, ECOG PS, LDH level, number of extra-nodal sites and IPI score could be used to predict the survival for patients with GI-DLBCL. A multivariate analysis was also performed to evaluate the prognosis between SCT and CTa and the results showed that treatment modality was not an independent prognostic factor. Therefore, as for GI-DLBCL, multi-factors should be evaluated to select treatment modality. Considering the impact of surgery on the quality of patients' life, unless there have surgical indications, such as combined obstruction, bleeding or perforation, or it's difficult to make a clear diagnosis before surgery, SCT might be adopted. For those who have been clearly diagnosed or with no surgical indications, CTa irecommended.

Some limitations are inherent in this study. First, because of the nature of this retrospective study other than a prospective randomized clinical trial, further validation of the results is necessity. Second, the sample size of the enrolled patients was fairly small, especially for those of the treatment modality in the GCB group. Therefore, a prospective randomized clinical trial with a larger number of GIDLBCL patients is needed to give a more reliable suggestion for the option of treatment strategy.

Conclusions

The study demonstrated that molecular phenotypes of GCB and non-GCB fail to predict survival for patients with GI-DLBCL. Patients treated with SCT seemed to have a higher survival rate in the whole cases and in the GCB phenotype, but it was not an independent prognostic index. Multi-factors should be evaluated to select treatment modality.

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Disclosure of conflict of interest

None.

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