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ORIGINAL ARTICLE

Lymphotoxin alfa and receptor-interacting protein kinase 1 gene polymorphisms may correlate with prognosis in patients with diffuse large B cell lymphoma treated with R-CHOP

Yee Soo Chae · Jong Gwang Kim · Sang Kyun Sohn · Joon Ho Moon · Shi Nae Kim · Su Jeong Lee · Tae-In Park · Myung-Hoon Lee

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Abstract
Purpose Diffuse large B cell lymphoma (DLBCL) is a heterogenous disease entity due to diverse clinical outcomes to treatment. Most anticancer agents, regardless of their distinct mechanisms of action, ultimately kill cancer cells by inducing apoptosis. Accordingly, the present study analyzed the impact of polymorphisms of apoptosis-related genes on outcome in DLBCL patient treated with R-CHOP.
Patients and methods Ninety patients with DLBCL treated with R-CHOP were enrolled in the present study. The genomic DNA was extracted from paraffin-embedded tissue and 22 polymorphisms of 18 apoptosis-related genes were assessed using a polymerase chain reaction–restriction fragment length polymorphism assay.
Results All the evaluable patients were responsive to R-CHOP. The multivariate analysis showed that the AA genotype of lymphotoxin alpha (LTA) C804A (rs1041981) and GG genotype of RIPK1 G83A (rs2272990) were significantly correlated with a worse time to progression (TTP) compared with the combined C/A and C/C genotype and the combined G/A and A/A genotype (hazard ratio [HR] = 7.92; 95% confidence interval [CI] = 1.42–44.18; $P = 0.018$ and HR = 20.02; 95% CI = 1.59–251.52; P value = 0.018, respectively), whereas no association was observed between the other polymorphisms and TTP.
Conclusion The polymorphisms of LTA (rs1041981) and RIPK1 (rs2272990) may correlate with TTP in patients with DLBCL treated with R-CHOP.

Keywords Diffuse large B cell lymphoma · R-CHOP · Apoptosis-related gene · Polymorphism · Prognosis

Y. S. Chae · J. G. Kim (✉) · S. K. Sohn (✉) · J. H. Moon · S. N. Kim · S. J. Lee
Department of Oncology/Hematology,
Kyungpook National University Hospital,
Kyungpook National University School of Medicine,
Daegu 700-721, Korea
e-mail: jkk21c@knu.ac.kr

S. K. Sohn
e-mail: sksohn@knu.ac.kr

T.-I. Park
Department of Pathology,
Kyungpook National University Hospital,
Kyungpook National University School of Medicine,
Daegu, Korea

M.-H. Lee
Technology Center for Diagnosis and Prediction,
Kyungpook National University School of Medicine,
Daegu, Korea

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), and cyclophosphamide/adriamycin/vincristine/prednisolone (CHOP) combination chemotherapy was considered the standard regimen until the rituximab era. Although rituximab (R)-CHOP has improved survival in the treatment of DLBCL [1–3], the mechanism of rituximab has not yet been clearly defined. Several theories have already been suggested, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and the induction of apoptosis, where the latter is also closely related with chemoresistance to DNA targeting agents, such as alkylators or topoisomerase inhibitors [4–6].

Apoptosis is a distinct mode of cell death that is responsible for the deletion of cells in normal tissues, and it also occurs in specific pathologic contexts. Apoptosis occurs

spontaneously in malignant tumors, often markedly retarding their growth, and it is also increased in tumors responding to irradiation, cytotoxic chemotherapy, heating, and hormone ablation [7]. Most anticancer agents, regardless of their distinct mechanisms of action, ultimately kill cancer cells by inducing apoptosis [7, 8]. Several studies have suggested that functional differences between polymorphic variants of apoptosis-related genes may alter their ability to bind components of the transcriptional machinery, activate transcription, induce apoptosis, and repress the transformation of primary cells [9–11]. However, few studies have investigated the predictive or prognostic value of these important polymorphisms for R-CHOP chemotherapy in patients with DLBCL.

Accordingly, the present study analyzed the polymorphisms of apoptosis-related genes and their impact on the response to chemotherapy and survival of patients with DLBCL treated with R-CHOP chemotherapy.

Patients and methods

Patients and treatment protocol

The current study comprised 90 DLBCL patients treated with R-CHOP as the frontline chemotherapy at Kyungpook National University Hospital (KNUH) between February 2004 and December 2007. The R-CHOP chemotherapy was administered as follows: rituximab 375 mg/m^2 was infused over 4–6 h on day 1 before starting the CHOP chemotherapy. The CHOP regimen consisted of an intravenous infusion of cyclophosphamide 750 mg/m^2, adriamycin 50 mg/m^2, vincristine 2 mg, and the oral administration of 100 mg prednisone on days 1–5, which was repeated every 3 weeks. The planned number of cycles was four cycles of R-CHOP followed by involved field radiation, or six cycles of R-CHOP for stages I or II disease and six or more for stages III or IV disease.

The response to chemotherapy was evaluated after the completion of two to three courses of chemotherapy, 1 month after the completion of all planed cycles, and then every 3 months. Written informed consent for gene expression analyses was received from the patients. This study was approved by the Institutional Research Board at Kyungpook National University Hospital, Daegu, Korea.

Selection of target gene polymorphisms

Owing to the huge number of single-nucleotide polymorphism (SNPs) in the human genome, the efficient selection of the SNPs most likely to contribute to phenotypic effects was the first challenge. Thus, a prioritizing strategy was created using public databases that provide diverse information on the potential phenotypic risks of SNPs. First, candidate genes involved in apoptosis and related information were collected from web-based databases that included information on the biological pathway and potential biologic effects of polymorphisms. The SNPs with frequencies lower than 0.1 were excluded based on the allele frequencies recorded for the East Asian population obtained from FASTSNP. The selected SNPs were then scored according to certain phenotypic risks, and ordered according to the sum of the risk scores. Finally, the SNPs with high risk scores were included in the current analysis.

Genotyping of apoptosis-related genes polymorphism

The genomic DNA was extracted from paraffin-embedded tumor-bearing tissue using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA). Twenty-two SNPs of 18 apoptosis-related genes [*FAS* (rs10788624 and 1800682), *LTA* (lymphotoxin alpha, rs1041981), *FASL* (FAS ligand, rs763110), *TNFSF10* (rs1131532), *TNFRSF1A* (rs767455), *TNFRSF10B* (rs1047266), *RIPK1* (receptor-interacting serine/threonine kinase 1, rs2272990), *AKT1* (rs1130233), *PTGS2* (rs5275), *TP53* (rs1042522), *BCL2* (rs1801018), *BCL2L11* (rs724710), *BID* (rs8190315), *CASP3* (rs2705897), *CASP6* (rs1042891 and rs2301717), *CASP7* (rs2227310), *CASP8* (rs3769818), and *CASP9* (rs4645978)] were then determined using a polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) assay as described in our previous study [12]. For quality control, the genotyping analysis was performed blind as regards the subjects. The selected PCR-amplified DNA samples ($n = 2$, for each genotype) were also examined by DNA sequencing to confirm the genotyping results.

Definitions

The responses were defined according to International Working Group criteria [13]. Overall survival (OS) was measured from day 1 of the first cycle of R-CHOP until the date of death or last follow-up. Time to progression (TTP) was calculated from day 1 of the first cycle of R-CHOP until treatment failure (disease progression or recurrence).

Statistical analysis

The genotypes for each SNP were analyzed as a three-group categorial variable (referent model), and also grouped according to the dominant and recessive model according to the results of Kaplan–Meier plotting. The differences in the TTP or OS according to the polymorphisms of the apoptosis-related genes were compared using log-rank tests. Cox's proportional hazard regression model was used for the

multivariate survival analyses, including the stage (stages 1, 2 vs. 3, 4), age (<60 vs. ≥60 years), performance status (ECOG 0, 1 vs. ≥2), LDH level (normal vs. beyond elevated), extranodal involvement (≤1 vs. ≥2 sites), and International Prognostic Index (IPI) score. The hazard ratio (HR) and 95% confidence interval (CI) were also estimated. A cutoff *P* value of 0.05 was adopted for all the statistical analyses. The statistical data were obtained using an SPSS software package (SPSS 15.0, Chicago, IL, USA).

Results

Patient characteristics and outcomes

The patient characteristics are summarized in Table 1. The median age was 58.5 (range 18–78) years and 51 (56.7%) patients were male. Twenty-nine (32.3%) patients had stages 3 and 4 disease according to the Ann Arbor classification system, and 23 (25.6%) patients had intermediate to high or high IPI scores.

The median number of R-CHOP cycles was 6 (range 3–8). Among the patients enrolled in the current study, two patients were unable to complete the planned cycles of R-CHOP due to severe infection and rituximab-induced pneumonitis. The response rate to R-CHOP was 100% among the 88 evaluable patients, where complete response (CR) was observed in 76 (86.4%) patients before radiotherapy. Involved field radiotherapy was given to 7 of 14 patients with stage I and 23 of 47 patients with stage II. During the median follow-up period of 27.4 (range 3.8–52.1) months for the 77 survivors, 10 (11.1%) patients experienced progression or relapse and three patients died from lymphoma.

Genotype and survival analysis

The frequencies of each genotype are shown in Table 2. Among the target SNPs, *CASP7* (rs2227310), *LTA* (rs1041981), *FAS* (rs1800682), *RIPK1* (rs2272990), and *BID* were found to deviate from the Hardy–Weinberg equilibrium ($P < 0.05$). No statistical associations were observed between the polymorphisms and the clinical parameters. An univariate analysis of the TTP after R-CHOP chemotherapy showed that the survival of the patients with the AA genotype of *LTA* C804A (rs1041981) was worse than the survival of the patients with the combined CC and CA genotype (HR = 6.22; 95% CI = 1.66–23.21), while the combined GA and AA genotype of *RIPK1* G83A (rs2272990) was marginally related to a better TTP than the GG genotype as the dominant A allele model (HR = 0.15; 95% CI = 0.02–1.18; $P = 0.072$; Fig. 1).

Table 1 Patient characteristics and clinical outcomes

	N (%)
Age	
Median, range	58.5, 18–78
≥60 years	44 (48.9)
Sex, male (%)	51 (56.7)
Stage	
I	14 (15.6)
II	47 (52.2)
III	14 (15.6)
IV	15 (16.7)
LDH, elevated (%)	39 (43.8)
Performance status (ECOG) ≥2	16 (17.8)
Extranodal involvement ≥2	11 (12.2)
International prognostic index (IPI)	
Low	54 (60.0)
Low intermediate	13 (14.4)
High intermediate	15 (16.7)
High	8 (8.9)
Marrow involvement	6 (6.7)
B symptom	13 (14.4)
Bulky	3 (3.3)
Response rate ($n = 88$)[a]	
CR	76 (86.4)
PR	12 (13.6)
Radiotherapy (IFRT)	30 (33.3)
Among stage I	7/14 (50.0)
Among stage II	23/47 (48.9)
Progression/relapse	10 (11.1)
Salvage treatment	5
High-dose methotrexate	2
ICE followed by Auto-SCT	2
Ibritumomab tiuxetan	1
Death	12 (14.3)
Recurrent lymphoma after R-CHOP	3
Infection and sepsis	6[b]
Pneumonitis	1
Bleeding	1
Unknown	1[c]
Median number of R-CHOP, range	6, 3–8
Median duration of follow-up, range (days)	27.4, 3.8–52.1

ECOG Eastern Cooperative Oncology Group, *IFRT* involved field radiation therapy, *ICE* ifosfamide/cisplatin/etoposide, *SCT* stem cell transplantation'

[a] Two patients were unable to complete the planned cycles due to severe infection and pneumonitis

[b] One patient died of sepsis in a state of complete remission during autologous SCT

[c] One patient died of unknown causes in a state of complete remission after autologous SCT

Table 2 Univariate analysis of time to progression (TTP) according to target SNPs

Genotype	*N*	Time to progression			Genotype	*N*	Time to progression		
		HR	95% CI	*P* value			HR	95% CI	*P* value
CASP3 (rs2705897)					*FAS* (rs10788624)				
TT	49	1.00	Reference		TT	30	1.00	Reference	
TG	32	0.57	0.12–2.79	0.491	TC	39	2.50	0.48–12.99	0.276
GG	2	NC[b]			CC	10	NC[b]		
TG + GG	34	0.50	0.10–2.42	0.388	TC + CC	49	1.61	0.32–8.21	0.569
CASP6 (rs1042891)					*FAS* (rs1800682)[a]				
CC	20	1.00	Reference		TT	17	1.00	Reference	
CT	27	1.25	0.11–13.86	0.857	TC	54	2.35	0.28–19.42	0.429
TT	34	3.58	0.42–30.26	0.240	CC	9	NC[b]		
CASP6 (rs2301717)[a]					*FASLG* (rs763110)				
GG	22	1.00	Reference		CC	61	1.00	Reference	
GT	51	2.98	0.37–24.02	0.305	CT	19	2.38	0.05–3.34	0.409
TT	12	1.74	0.11–27.92	0.697	TT	3	NC[b]		
CASP7 (rs11593766)					CT + TT	21	0.38	0.05–3.06	0.362
TT	77	1.00	Reference		*TNFSF10* (rs1131532)				
TG	3	NC[b]			CC	35	1.00	Reference	
GG	0				CT	38	0.86	0.20–3.60	0.831
CASP7 (rs2227310)[a]					TT	11	NC[b]		
GG	11	1.00	Reference		*TNFRSF1A* (rs767455)				
GC	64	0.41	0.08–2.17	0.295	TT	58	1.00	Reference	
CC	9	0.58	0.05–6.55	0.663	TC	25	0.66	0.14–3.13	0.600
CASP8 (rs3769818)					CC	4	NC[b]		
CC	58	1.00	Reference		*TNFRSF10B* (rs1047266)				
CT	22	2.14	0.60–7.65	0.240	CC	32	1.00	Reference	0.518
TT	5	NC[b]			CT	40	0.40	0.10–1.82	0.252
CT + TT	27	1.49	0.42–5.29	0.536	TT	7	NC[b]		
CASP9 (rs1052571)					*AKT1* (rs1130233)				
TT	25	1.00	Reference		GG	16	1.00	Reference	
TC	43	0.94	0.22–4.00	0.937	GA	45	0.22	0.04–1.15	0.072
CC	11	0.69	0.07–6.63	0.745	AA	16	0.67	0.13–3.39	0.626
CASP9 (rs4645978)					*BCL2* (rs1801018				
AA	75	1.00	Reference		AA	70	1.00	Reference	
AG	5	2.13	0.27–17.20	0.477	AG	11	1.30	0.28–6.18	0.738
GG	0				GG	1	NC[b]		
LTA (2272990)[a]					*BCL2L11* (rs724710)				
CC	14	1.00	Reference	0.025	CC	65	1.00	Reference	
CA	50	0.99	0.11–8.86	0.993	CT	12	1.60	0.32–8.11	0.570
AA	9	6.16	0.70–55.25	0.040	TT	2	16.56	1.02–269.48	0.049
CC + CA	64	1.00	Reference		CT + TT	14	2.34	0.30–19.23	0.234
AA	9	6.22	1.66–23.21	<0.001	*RIPK1* (rs2272990)[a]				
TP53 (rs1042522)					GG	47	1.00	Reference	
GG	27	1.00	Reference	0.439	GA	24	0.22	0.03–1.75	0.152
GC	45	1.52	0.18–12.6	0.697	AA	10	NC[b]		
CC	9	0.39	0.02–6.85	0.523	GA + AA	34	0.15	0.02–1.18	0.072
GC + CC	54	3.69	0.45–30.35	0.224	*PTGS2* (rs5275)				

Table 2 continued

Genotype	*N*	Time to progression			Genotype	*N*	Time to progression		
		HR	95% CI	*P* value			HR	95% CI	*P* value
BID (rs8190315)[a]					TT	52	1.00	Reference	
AA	73	1.00	Reference		TC	26	0.97	0.24–3.89	0.961
AG	8	2.88	0.57–14.60	0.202	CC	2	NC[b]		
GG	2	NC[b]							
AG + GG	10	0.29	0.57–14.60	0.202					

[a] Genotype distribution deviated from Hardy–Weinberg equilibrium ($P < 0.05$)

[b] Not computable

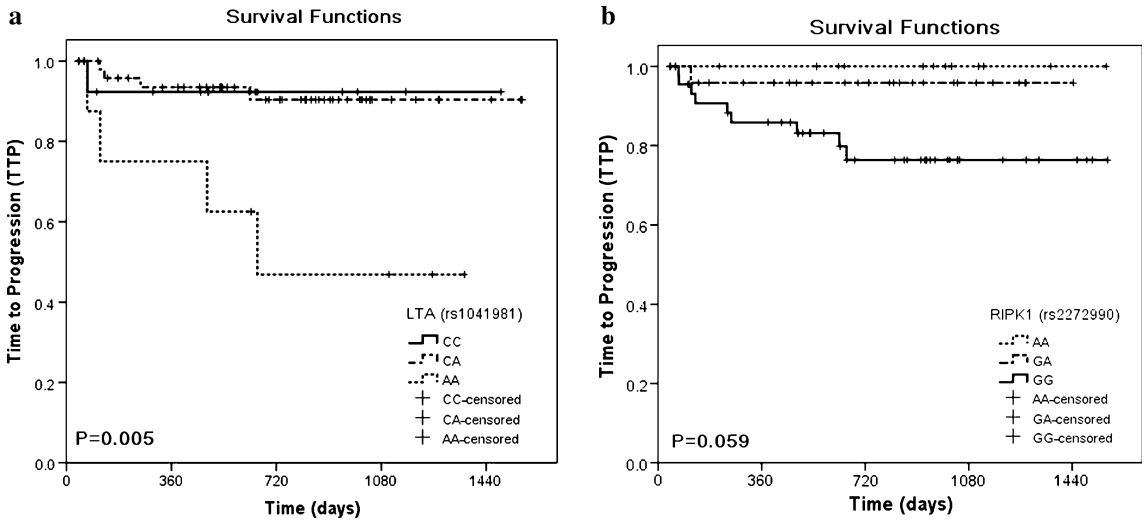

Fig. 1 Kaplan–Meier curves of TTP according to *LTA* C804A and *RIPK1* G83A SNPs. **a** *LTA* C804A (rs1041981), **b** *RIPK1* G83A (rs2272990)

A multivariate survival analysis also showed that the *LTA* C804A (rs1041981) and *RIPK1* G83A (rs2272990) polymorphisms were significantly associated with the TTP, where the AA genotype of *LTA* C804A (rs1041981) and GG genotype of *RIPK1* G83A (rs2272990) were unfavorable predictive markers for DLBCL treated with RCHOP (HR = 7.92; 95% CI = 1.42–44.18; $P = 0.018$ and HR = 20.02; 95% CI = 1.59–251.52; $P = 0.020$, respectively), along with the IPI (Table 3). However, no association was observed between these two polymorphisms and OS.

Table 3 Multivariate analysis of risk factors for TTP

	TTP		
	HR	95.0% CI	*P* value
Sex, female (vs. male)	0.15	0.01–2.36	0.179
IPI (vs. low risk)			0.052
Low intermediate	2.28	0.20–25.57	0.504
High intermediate	7.56	1.19–48.01	0.032
High	14.57	1.65–128.58	0.016
B symptoms	2.08	0.20–22.02	0.542
Bulky disease	6.88	0.40–118.48	0.184
Genotype			
LTA C804A (rs1041981), AA (vs. CC + CA)	7.92	1.42–44.18	0.018
RIPK1 G83A (rs2272990), GG (vs. GA + AA)	20.02	1.59–251.52	0.020

Discussion

The prognostic impact of polymorphisms of apoptosis-related genes was investigated in DLBCL patients treated with R-CHOP. As a result, the current study demonstrated that the AA genotype of *LTA* C804A (rs1041981) and GG genotype of *RIPK1* G83A (rs2272990) are unfavorable predictive markers for the TTP, along with the IPI. Considering the homogenous ethnic background of Korean patients, any potential confounding effect due to ethnicity is likely to be small in the present study.

Most chemotherapeutic drugs, also used in the treatment of lymphoma, primarily induce cell death via the induction of the stress-induced apoptosis pathway [14–16], and activated apoptosis has already been recognized as the main active mechanism of rituximab for B cell lymphoma [17]. In addition, previous studies have suggested that the intrinsic sensitivity of lymphoma cells to apoptosis plays an important role in the response to chemotherapy and eventual clinical outcome for patients with lymphoma [18, 19],

which has also been supported by several studies showing an association between the expression of apoptosis-related proteins and prognosis in lymphoma patients treated with chemotherapy. [20–23] One important biological determinant engaged in apoptosis is the activation pathway of nuclear factor-kB (NF-kB), which can translocate into the cell nucleus and bind to specific sequences in the promoter or enhancer regions of target inflammatory genes and other genes related to cell growth, differentiation, apoptosis, and cancer development [24]. The NF-kB pathway is activated by triggering various receptor-mediated pathways, including the TNF superfamily, such as TNF-α or lymphotoxin-α (LTA or TNF-β) and RIPK, although the activation mechanism remains to be unknown in DLBCL [25].

Lymphotoxin alpha is a pro-inflammatory cytokine and member of the TNF family that plays a key role in communication between lymphocytes and stromal cells, and the polymorphism *LTA* G252A in the coding lesion has already been presented as a prognostic factor of NHL [26, 27]. In the current study, the homozygote of the A allele of *LTA* C804A (rs1041981) was found to be associated with a poor prognosis for DLBCL, however, the opposite findings related to cancer susceptibility were previously reported in two other case–control studies of other solid tumors. Takei et al. [28] demonstrated that the CA + AA genotype of *LTA* C804A (rs1041981) was associated with a significantly lower presence of male lung cancer than the CC genotype (adjusted OR = 0.60, 95% CI = 0.37–0.97), while Niwa et al. [29] showed that the CA + AA genotype of *LTA* C804A (rs1041981) was associated with a lower incidence of endometrial cancer (adjusted OR = 0.50, 95% CI = 0.28–0.89) as the dominant A allele model. Nonetheless, other studies have demonstrated that the A allele of *LTA* C804A (rs1041981), with a changed amino acid residue from threonine to asparagines (Thr26Asn), is associated with more transcripts or higher protein levels of LTA and cell adhesion molecules [30, 31], which may induce apoptosis via the activation of lymphocytes or activate lymphoma cells directly. Although the impact of *LTA* gene polymorphisms on the prognosis of certain malignancies would appear to be diverse, these differences may be partially explained by the multifunctional effect of LTA, which can promote cell growth and adhesion, while also influencing the growth of certain tumors, such as lymphoid malignancies.

RIPK1, activated by interaction between the TNF superfamily and its receptors, is also an essential element in the signal transduction of TNF-induced NK-κB activation in B cells [32]. Although the role of *RIPK1* polymorphisms has not yet been fully clarified or evaluated in cancers, *RIPK1* variants have been implicated in the development of Wegener's granulomatosis based on the altering apoptosis [33]. As such, the results of the current study indicate that *RIPK1* polymorphisms may be related to the alteration of NF-κB activation in the apoptosis or immune response of lymphoma cells. Moreover, the TNF/RIP signaling pathway would appear to be an important prognostic component in DLBCL patients treated with R-CHOP.

Some SNPs were found to deviate from the HWE in the current study, and three possible causes are suggested: a genotyping error, the small sample size, or DNA extracted from tumor tissue. Thus, the deviated genotypes were first confirmed by direct sequencing; plus, the genotypes of two SNPs tested from tumor tissue were compared with those from the DNA of lymphoma-free BM biopsy samples taken at the initial diagnosis from 12 patients, and both genotypes were identical. Accordingly, it would appear that the deviation was caused by the small sample size, although it is still possible that somatic alteration in the process of tumorigenesis could have caused the deviation. Furthermore, the patients enrolled in the current study had a good IPI, which may have caused a better response to the R-CHOP treatment. Therefore, the present results have some limitations as regards drawing a definite conclusion due to the small sample size and extracted DNA samples.

In conclusion, the present study suggests that the polymorphisms of *LTA* C804A (rs1041981) and *RIPK1 G83A* (rs2272990) can be considered as predictive markers for DLBCL patients treated with R-CHOP. However, further studies are warranted to clarify the role of apoptosis-related gene polymorphisms as a predictive or prognostic biomarker in patients with DLBCL.

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