Research Article

Gemcitabine, Dexamethasone, Cisplatin with Rituximab in Treatment Transplant- Ineligible Relapsed Non-Hodgkin B-cell Lymphoma Patients

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Abstract

We conducted this study to find out the effectiveness of treatment as well as some prognostic factors when using R-GDP (Rituximab- Gemcitabine, Dexamethasone, and Cisplatin) regimen to treat transplant-ineligible relapsed non-Hodgkin B-cell lymphoma patients. 49 patients diagnosed with relapsed non-Hodgkin B-cell lymphoma treated with R-GDP (Rituximab- Gemcitabine, Dexamethasone, and Cisplatin) regimen were retrospectively analyzed. Patients who subsequently underwent autologous stem cell transplantation were excluded. After 2 cycles, ORR was 71.4%: CR: 12 patients (24.5%), PR: 23 patients (46.9%). 14 patients (28.6%) who did not achieve at least PR would be treated with another regimen. After 6 cycles, CR was 38.8% (19 patients). Median OS and PFS were 36 and 32 months; respectively. The 5-year rates were 36.4 % and 18.1% for OS and PFS; respectively. No serious side effects were reported. Neutrophilia and thrombocytopenia were grade 3, and grade 2; respectively. Univariate and multivariate analysis showed that LDH ≥237 U/L was an independent adverse prognostic factor for OS (*P*=0.003, HR: 6.256, 95% CI: 1.900- 20.602), BCL6 positive and LDH ≥ 237 U/L were an independent adverse prognostic factors for PFS (*P*=0.047, HR: 3.651, 95% CI: 1.020- 13.074; *P*=0.049; HR: 3.707, 95% CI: 1.004- 13.678; respectively). R-GDP is effective and has less toxicity in the treatment of transplant-ineligible relapsed non-Hodgkin B cell lymphoma patients, LDH ≥237 U/L is an independent adverse prognostic factor for OS and PFS, while BCL6 positive are independent adverse prognostic factors for PFS.

Keywords: *Relapsed lymphoma, Non-Hodgkin B cell lymphoma, Gemcitabine, R-GDP, Transplant-ineligible*

Introduction

Relapsed non-Hodgkin lymphoma treatment remains challenging.[1, 2] The most recognized standard regimen for the treatment of relapsed lymphoma is stem cell transplantation after high-dose chemotherapy such as ICE (ifosphamid, carboplatin, and etoposide), DHAP (dexamethasone, high-dose cytarabine, and cisplatin), ESHAP (etoposide, methylprednisolon, cytarabine, and cisplatin), in combination with rituximab if the patient has positive CD20.[3, 4] These regimens have a relatively high response rate but have limitations due to high toxicity, especially with high-dose cytarabine-containing regimens.[3-6] In general, it is probably only suitable for patients who have subsequently received an autologous stem cell transplant. For patients who are not eligible for stem cell transplantation, treatment after relapse is quite difficult. There is some research focusing on new active agents such as new antibodies, selinexor, ADC (antibody-drug conjugates), or CAR T cells.[7-9] Some clinical studies have shown that combinations of novel antibodies as atezolizumab with obinutuzumab, or a combination of new antibodies with targeted drugs as obinutuzumab with ibrutinib, or alone as blitunamumab, are also effective.[10-12] However, they are quite difficult to apply in developing countries due to the high cost. Other studies seek directions in the combination of available drugs. Gemcitabine is one of those directions. Gemcitabine has excellent antitumor activity against a wide spectrum of solid human tumors.[13] Gemcitabine alone or in combination, and how to get the most effectiveness is a question that requires more research to answer. Ahn *et al.* suggested that gemcitabine alone was effective even in relapsed/refractory T/NK lymphoma.[14] According to several randomized trials, no salvage regimen was superior, in comparison with R-GDP (rituximab plus gemcitabine, dexamethasone, and cisplatin). Mi *et al.* compared the efficacy and toxicity of GDP

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with ICE and showed that they were equivalent in efficiency.[15] Crump *et al*., and Hafez *et al*. showed that the patients with relapsed/refractory lymphoma treated with GDP had non-inferior survival, less toxicity, and better quality of life than those treated with DHAP.[16, 17] However, there is still controversy. Zlonick *et al*. showed the limited effectiveness of gemcitabine in the treatment of relapsed lymphoma.[18] Smith suggested that it is early to eliminate gemcitabine.[19] Gutierrez also agreed that there should be more gemcitabine-based regimens for non-Hodgkin lymphoma relapsed.[20]

Therefore, we conducted this study to find out the effectiveness of treatment as well as some prognostic factors when using an R-GDP regimen to treat transplant-ineligible relapsed non-Hodgkin B-cell lymphoma patients.

Materials and Methods

Patients

From March 2013 to September 2019, at the Center of Hematology and Blood Transfusion, in Bach Mai Hospital, Hanoi, Vietnam, 49 patients diagnosed with relapsed non-Hodgkin B-cell lymphoma treated with the R-GDP (Rituximab- Gemcitabine, Dexamethasone, and Cisplatin) regimen were retrospectively analyzed. The diagnosis was based on the HE stain and immunohistochemical stain with the marker: CD20, CD19, CD79a, CD3, CD5, CD23, CD10, MUM1, BCL6, and BCL2. Patients who subsequently underwent autologous stem cell transplantation were excluded.

Treatment

R-GDP consistent with gemcitabine (1,000 mg/m^2) intravenous (IV) on days 1 and 8; cisplatin (75 mg/m^2) IV on day 1; rituximab 375 mg/m^2 IV on day 2; dexamethasone 40 mg IV on days 1-4; a cycle was administered every 3 weeks, for a total of six cycles. The response to chemotherapy was evaluated after 2 cycles; patients who did not achieve at least partial remission would be treated with another regimen.

Definition

The diagnosis was defined according to the WHO 2008 classification of hematopoietic and lymphoid tumors.[21] The stage was classified according to the Ann Arbor Stage. Response to chemotherapy was determined according to the criteria of the International Working Group (RECIL 2017).[22] Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria.[23]

Statistics analysis

OS (Overall survival) was defined as the time from diagnosis of relapse to the last follow-up, or death. PFS (Progressing free survival) was defined as the time from the beginning of treatment to further progression of the disease, or death. The ROC curve (receiver operating characteristic) was used to separate for the LDH level to achieve a predictive value for OS and PFS. The cutoff value of the LDH level was 237 U/L. Univariate (using the Kaplan-Meyer method) and multivariate (using the Cox proportional hazards model) survival analyses were evaluated in OS and PFS for variables such as risk factors: age >65, time of relapse (≤12 months), type of lymphoma, non-GCB (non- germinal center B cell) type, BCL2 positive, BCL6 positive and LDH ≥237 U/L. P<0.05 was considered a significant statistical difference.

Results and Discussion

Patients characteristic

49 patients included 38 men (77.6%). The median age was 59 years (from 29 to 80). The laboratory indices and characteristics of the patients are shown in **Tables 1 and 2**. 61.2 % of the patients with a diagnosis of diffuse large B cell lymphoma (DLBCL) represent the highest percentage. In the group of patients with DLBCL, the non-GCB type was 20.4%, GCB type was 40.8%.

Table 1. Laboratory Indices of Patients

	N	Minimum	Maximum	Mean	Std. Deviation
HGB (g/L)	49	69	160	117.00	21.495
WBC (x10^9 /L)	49	1.74	17.20	6.8994	2.98717
Platelet (x10^9 /L)	49	31	510	230.69	102.827
Ferritin (ng/mL)	49	8.40	4033.00	769.8735	781.93884
LDH (U/L)	49	118	1183	284.59	182.595
Ure (mmol/L)	49	2.80	22.10	6.2673	2.94593
Creatinin (mmol/L)	49	48	213	85.88	27.404
GOT (U/L)	49	2	99	33.06	18.873
GPT (U/L)	49	7	186	33.22	34.431
Valid N (listwise)	49				

Treatment outcome

After 2 cycles, ORR (included CR and PR) was 71.4% with 35 patients: CR: 12 patients (24.5%), PR: 23 patients (46.9%). 14 patients (28.6%) who did not achieve at least PR (included SD and relapse) would be treated with another regimen, **(Table 3)**. After 6 cycles, the CR was 38.8% (19 patients), **(Table 3)**. The median OS and PFS were 36 and 32 months, respectively **(Table 4)**. The 5-year rates were 36.4 % and 18.1% for OS and PFS; respectively **(Table 4)**.

Unvariate and multivariate analysis showed that LDH 237≥ U/L was an independent adverse prognostic factor for OS (*P*=0.003, HR: 6.256, 95% CI: 1.900- 20.602); BCL6 positive, and LDH ≥ 237 were independent adverse prognostic factors for PFS (*P*=0.047, HR: 3.651, 95% CI: 1.020- 13.074; *P*=0.049; HR: 3.707, 95% CI: 1.004- 13.678; respectively) **(Table 5, Figures 1 and 2)**.

Table 2. Characteristics of Patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Sex	Male	38	77.6	77.6	77.6
	Female	11	22.4	22.4	100.0
	Total	49	100.0	100.0	
Type	DLBCL	30	61.2	61.2	61.2
	SLL	6	12.2	12.2	73.5
	FL	2	4.1	4.1	77.6
	Mantle cell lymphoma	6	12.2	12.2	89.8
	Marginal zone lymphoma	2	4.1	4.1	93.9
	MALT lymphoma	2	4.1	4.1	98.0
	Lymphocyticplasmacytoid	1	2.0	2.0	100.0
	Total	49	100.0	100.0	
Time of relapse	≤12 months	5	10.2	10.2	10.2
	>12 months	44	89.8	89.8	100.0
	Total	49	100.0	100.0	
B syndromes	No	14	28.6	28.6	28.6
	Yes	35	71.4	71.4	100.0
	Total	49	100.0	100.0	
Lymphadenopathy	No	5	10.2	10.2	10.2
	Yes	44	89.8	89.8	100.0
	Total	49	100.0	100.0	
Extranodal Involvement	No	27	55.1	55.1	55.1
	Yes	22	44.9	44.9	100.0
	Total	49	100.0	100.0	
Hepatomegaly	No	42	85.7	85.7	85.7
	Yes	7	14.3	14.3	100.0
	Total	49	100.0	100.0	
Splenomegaly	No	34	69.4	69.4	69.4
	Yes	15	30.6	30.6	100.0
	Total	49	100.0	100.0	
Bone Marrow Involvement	No	34	69.4	69.4	69.4
	Yes	15	30.6	30.6	100.0
	Total	49	100.0	100.0	
Ann Arbor Stage	II	4	8.2	8.2	8.2
	III	6	12.2	12.2	20.4
	IV	39	79.6	79.6	100.0
	Total	49	100.0	100.0	
GCB (germinal centre B-cell)	Yes	10	20.4	33.3	33.3
	No	20	40.8	66.7	100.0
	Total	30	61.2	100.0	
Previous Protocol	R-CHOP	45	91.8	91.8	91.8
	CHOP	3	6.1	6.1	98.0
	COP	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Note: DLBCL: diffuse large B cell lymphoma, SLL: small lymphocytic lymphoma, FL: follicular lymphoma, MALT: mucosa-associated lymphoma tissue

Table 3. Response to chemotherapy

Cycles	Response Rate		Frequency	Percent	Valid Percent	Cumulative Percent
After 2 cycles	ORR	CR	12	24.5	24.5	24.5
		PR	23	46.9	46.9	71.4
	SD		7	14.3	14.3	85.7
	Relapse		7	14.3	14.3	100.0
	Total		49	100.0	100.0	

After 6 cycles	ORR	CR	19	38.8	54.3	54.3
		PR	16	32.7	45.7	100.0
	Total		35	71.4	100.0	

Note: ORR: overall response rate, CR: complete response, PR: partial response, SD: stable disease

Table 4. Overall survival (OS) and Progressing – free survival (PFS) follow in 5 years

Survival Time	Mean (95% Confidence Interval)				Median (95% Confidence Interval)				5 year rate
	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound	
PFS (months)	32.761	3.728	25.453	40.069	32.000	6.835	18.603	45.397	18.1%
OS (months)	42.832	4.570	33.874	51.790	36.000	10.145	16.115	55.885	36.4%

Table 5. Prognostic factor for Overall survival (OS) and Progressing – free survival (PFS)

Factors	Univariate analysis (OS)	Multivariate analysis (OS)		
	$P^{\text{Log-rank}}$ value	HR	95%CI	P^{Cox} value
Age >65 years	0.104			
Time of relapse ≤12 months	0.113			
Type of lymphoma	**0.047**			0.831
Non- GCB	0.675			
Bcl2 positive	0.467			
Bcl6 positive	0.057			
LDH≥237 U/L	**0.003**	6.256	1.900- 20.602	**0.003**
Factors	Univariate analysis (PFS)		Multivariate analysis (PFS)	
	$P^{\text{Log-rank}}$ value	HR	95% CI	P^{Cox} value
Age >65 years	0.606			
Time of relapse ≤12 months	0.272			
Type of lymphoma	0.082			
Non- GCB	0.636			
Bcl2 positive	0.233			
Bcl6 positive	**0.026**	3.651	1.020- 13.074	**0.047**
LDH≥237 U/L	**0.001**	3.707	1.004- 13.678	**0.049**

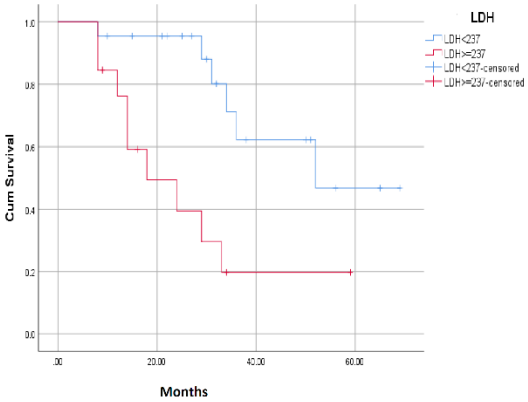

Figure 1. OS (Overall survival) according to the LDH level (≥237 U/L *vs* <237 U/L)

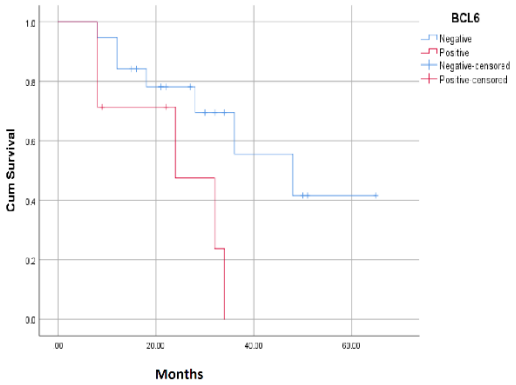

Figure 2. PFS (Progressing free survival) according to the presence of BCL6 (positive *vs* negative)

Toxicity

No serious side effects were reported. Toxicity was mainly in the hematologic system. Neutropenia grades 1, 2, 3, and 4 were recorded in 16.2%, 10.3%, 38.8% and 24.5%; respectively. Thrombocytopenia grades 1, 2, and 3 were reported in 14.3%, 30.6%, 22.4%; respectively. No neurotoxicity was observed. No patient had to delay chemotherapy and no dose was reduced due to toxicity.

It is difficult to provide specific and uniform guidelines in the treatment of patients with relapsed cancer in general, as well as relapsed lymphoma in particular. The guidelines only offer several solutions to choose from. Even choosing a pretransplant regimen for eligible transplantation patients has been difficult, let alone ineligible transplantation patients.

Recent modern studies support the use of new drugs in patients with relapsed lymphoma who are ineligible for transplantation.[24-26] These studies show positive results but are difficult to apply in developing countries.

Gemcitabine is an analog of cytidine with a structure similar to cytarabine, but it has advantages over cytarabine.[13] Studies have shown that cytarabine needs to be replaced with gemcitabine to achieve efficiency and have yielded positive results.[15-17] Gemcitabine alone or in combination with other cytotoxic agents such as R-GDP (rituximab- gemcitabine, cisplatin, and dexamethasone) has a role in the treatment of relapsed lymphoma. Crump *et al*., Rybka *et al*., and Moccia *et al*. showed a gemcitabine-based regimen as R-GDP was effective and well tolerated in patients with relapsed/refractory lymphoma.[15, 27, 28] Therefore, an equally effective regimen with less toxicity than R-GDP may be appropriate for transplant-ineligible patients.

Hou *et al*. evaluated the efficacy of R-GDP in relapsed/ refractory aggressive B-cell Non-Hodgkin Lymphoma and showed after two cycles that ORR was 72.0%, 2-year OS and PFS were 70.0% and 48.0%, respectively.[29] Chiu *et al*. retrospectively analyzed transplant-ineligible patients treated with a gemcitabin-based regimen and showed ORR was 33%, EFS was 4.0 months, and OS was 18 months.[30] In our study, after 2 cycles, ORR was 71,4%, after 6 cycles, CR was 38.8%. On the other hand, the results for OS and PFS were positive. The median OS and median PFS were 32 months and 36 months; respectively. The 5-year rates were 36.4 % and 18.1% for OS and PFS; respectively.

Our study also showed that the R-GDP regimen has less toxicity. No serious advents were reported. Neutrophilia and thrombocytopenia were almost 3 or 2 grade. This result is similar to studies by Batgi *et al*., and Ghio *et al*.[31, 32]

We were also interested in prognostic factors. The prognosis of newly diagnosed lymphoma has been determined for each subtype. IPI (International Prognostic Index) for DLBCL, FILPI (Follicular Lymphoma International Prognostic Index) for FL (Follicular Lymphoma), and MIPI (Mantle Cell Lymphoma International Prognostic Index) for mantle cell lymphoma. However, for relapsed status, new prognostic factors must be evaluated. However, prognostic factors also change depending on the treatment regimen. For example, for FL, after the rituximab era, the prognostic system changed from FLIPI to FLIPI2.[33] Therefore, we try to understand some more prognostic factors in the group of patients treated with R-GDP. The results of the univariate and multivariate analysis showed that LDH 237 ≥ U/L is an adverse factor for both OS and PFS, while BCL6 is an adverse factor for PFS. We also tried to find out if the time of relapse ≤12 months and the types of lymphoma were significant, but so far no association was found.

Our study has some limitations. The number of patients is not much, the type of lymphoma is not homogeneous, nor can it be divided into groups to evaluate the difference because the number of each group is small.

Conclusion

R-GDP is effective and has less toxicity in the treatment of transplant-ineligible relapsed non-Hodgkin B cell lymphoma patients, LDH ≥237 U/L is an independent adverse prognostic factor for OS and PFS, while BCL6 positive are independent adverse prognostic factors for PFS.

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Conflict of interest

None.

Financial support

None.

Ethics statement

The study protocol was approved by the Ethical Committee at Hanoi Medical University (no.187). Patient consent was waived by the committee as this study was a retrospective observational study.

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