

Original Article

Efficacy of rituximab combined with lenalidomide in patients with recurrent follicular lymphoma

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Abstract: Objective: To study the short-term and long-term efficacy of rituximab combined with lenalidomide in patients with recurrent follicular lymphoma (FL). Methods: A total of 60 recurrent FL patients were recruited and randomly assigned to the control group (n=30) and an observation group (n=30). The control group received rituximab combined with CHOP chemotherapy regimen, while the observation group received lenalidomide. The overall response rate (ORR) and incidences of adverse events were compared between the two groups after 6 cycles of chemotherapy, and with a follow-up time of 3 years; the 1-, 2-, and 3-year progression-free survival (PFS) and overall PFS, as well as the 1-, 2-, 3-year survival and overall survival were compared between the two groups. Results: The ORR of the observation group was significantly higher than that of the control group ($P<0.05$), and the incidences of adverse events showed no significant differences between two groups (all $P>0.05$); the 2- and 3-year PFS and survival, as well as the overall PFS and survival were all significantly higher in the observation than those in the control group (all $P<0.05$). Conclusion: The combined therapy of rituximab and lenalidomide for patients with recurrent FL improves ORR, and also effectively controls the progression of disease, prolongs the survival period of patients, and offers good safety. This therapy can be a new option of treatment for recurrent FL.

Keywords: Rituximab, lenalidomide, recurrent follicular lymphoma, short-term and long-term efficacy

Introduction

As a common malignant hematological cancer, non-Hodgkin's lymphoma (NHL) belongs to hematopoietic and lymphoid malignancies and originates in B cells, T cells and natural killer T (NKT) cells. The malignancy mainly occurs in the lymphatic organs including the thymus, lymph nodes, and spleen, as well as in extranodal lymphatic tissues and organs [1]. Follicular lymphoma (FL) is a common type of NHL that is derived from germinal center B cells, accounting for about 22.0% of the NHL in Europe and America, and about 5.9-7.0% in China [2]. FL is an indolent malignant lymphoma that can invade multiple lymph nodes, and it is characterized by painless swollen lymph nodes. FL can be definitely diagnosed by biopsy and is sensitive to chemoradiotherapy. However, a previous study found that a first-line therapy such as CHOP chemotherapy regimen had a high clinical benefit rate in the short term, but patients are prone to recurrence of disease and

even refractory or aggressive lymphomas that increase the difficulty of clinical treatment, shorten survival period and cause various lethal complications and even death, threatening the patient's life and health [3]. Treatment of recurrent FL has long been an intractable problem. In recent years, the development of targeted therapy has opened up new treatment options for FL patients. As a targeted therapy drug, and human-mouse chimeric anti-CD20 monoclonal antibody, rituximab induces immunological cytotoxicity in CD20-positive B lymphocytes by complement- and antibody-mediated cytotoxicity [4]. The drug was originally approved by the US in 1997 for patients with relapsed or refractory FL and chronic lymphocyte leukemia. Lenalidomide is a targeted therapy drug with immunomodulatory function, disrupting the function of intercellular adhesion molecules, neovascularization and cytokine expression, inhibiting osteoclast activation and myeloma cell proliferation, and induces cell apoptosis. This drug is mainly used for the treatment of

multiple myelomas and has proven effective for FL treatment [5]. At present, there is no standard treatment regimen for recurrent FL. Although targeted therapy drugs such as rituximab and lenalidomide have been used, there is still a lack of a clear standard in terms of their therapeutic efficacy and usage. In this study, the efficacy of the combined use of rituximab and lenalidomide for recurrent FL was reported to provide reference for clinical treatment.

Materials and methods

General information

A total of 60 recurrent FL patients, admitted to The Second Hospital of Shanxi Medical University from February 2010 to December 2015, were randomly assigned into the control group and the observation group at a 1:1 ratio. The control group received rituximab combined with CHOP-chemotherapy regimen, and the observation group received lenalidomide in addition. All patients signed the informed consent form, and the study was approved by the Ethics Committee of The Second Hospital of Shanxi Medical University.

Inclusion criteria: patients who met the relevant diagnostic criteria of recurrent FL and were aged ≥ 18 years [6]; patients with grade 1, 2, or 3a lymphomas according to the WHO classification of lymphoma; patients with no history of allergy to the study drugs; patients who had not received rituximab or lenalidomide within 6 months prior to the study; patients who were willing to participate in this study and signed the informed consent form.

Exclusion criteria: patients who had extranodal invasion; patients complicated with AIDS, hepatitis B and other infectious diseases; patients complicated with severe cardiovascular and cerebrovascular diseases or dysfunctions of liver, kidney and lung; patients complicated with other types of leukemia or malignant tumors, patients who did not completed treatment or had incomplete follow-up data.

Methods

Prior to chemotherapy, both groups received routine hydration and urinary alkalinization, and tropisetron was administered orally as an antiemetic.

The control group was given CHOP chemotherapy regimen combined with rituximab (Roche Diagnostics GmbH, Germany, 10 mL/100 mg): prednisone (Zhejiang Xianju Pharmaceutical Co., Ltd., China, 1 mL/25 mg) 100 mg/d, intravenous guttae (ivgtt) on days 1-5 + rituximab 375 mg/(m².d), ivgtt on day 1 + cyclophosphamide (Shanxi Zhendong Taisheng Pharmaceutical Co., Ltd., 200 mg) 750 mg/(m².d), ivgtt on day 2 + epirubicin (Zhejiang Hisun Pharmaceutical Co., Ltd., 10 mg) 60 mg/(m².d), ivgtt on day 2 + vincristine (Hisun-Pfizer Pharmaceuticals Co., Ltd., 1 mg) 1.4 mg/(m².d), ivgtt on day 2, repeat cycle every 21 days for 6 cycles. For the observation group, lenalidomide (Celgene Corporation, U.S.) was administered orally to the patients on the above basis at a dose of 15 mg/d on weeks 1-3 for 6 cycles (4 weeks as a cycle). All patients received 6 cycles of chemotherapy, during which measurements of routine blood tests were closely followed and granulocyte-colony stimulating factor was promptly given when white blood cell count (WBC) $< 2 \times 10^9/L$ or absolute neutrophil count (ANC) $< 1 \times 10^9/L$.

Outcome measures

The overall response rate (ORR) after 6 cycles of chemotherapy was compared in both groups and classified as complete response (CR), partial response (PR), stable disease (SD), and progression of disease (PD) according to the response evaluation criteria in lymphoma [7]. CR is defined as the complete resolution of all target lesions as indicated by PET-CT with negative results from bone marrow biopsy or fine-needle aspiration, liver and spleen impalpable and no enlarged lymph nodes. PR is defined as a reduction of the sum of the products of the longest perpendicular diameters (SPD) of 6 largest lesions by $\geq 50.0\%$, with no further enlargement in liver and spleen and no further lymph node metastasis. SD is defined as changes of SPD of the 6 largest lesions ranging from an increase of $\leq 25.0\%$ or a decrease of $< 50.0\%$. PD is defined as the appearance of new lesions after treatment and an increase of SPD of 6 largest lesions by $\geq 25.0\%$. ORR = (cases of CR + cases of PR)/total cases $\times 100.0\%$.

The two groups were compared in the incidence and grading of adverse events such as neutropenia, reduced platelet count, rash, thrombo-

Table 1. Comparison of baseline characteristics

	The control group (n=30)	The observation group (n=30)	t/ χ^2	P
Sex (male/female)	17/13	18/12	0.072	0.795
Mean age (years)	49.30±10.40	51.10±10.60	0.659	0.513
Time to progression (years)	1.59±0.38	1.62±0.41	0.385	0.770
Grading (n, %)			0.077	0.781
Grade 1	6 (20.00)	6 (20.00)		
Grade 2	10 (33.33)	9 (30.00)		
Grade 3a	14 (46.67)	15 (50.00)		
12 treatment cycles before recurrence (n, %)	29 (96.67)	27 (90.00)	1.078	0.302

Table 2. Comparison of efficacy of chemotherapy

	CR	PR	SD	PD	ORR (%)
The control group (n=30)	11 (36.67)	9 (30.00)	6 (20.00)	4 (13.33)	66.67
The observation group (n=30)	15 (50.00)	10 (33.33)	3 (10.00)	2 (6.67)	83.33
χ^2					6.193
P					0.027

CR: complete response; PR: partial response; SD: stable disease; PD: progression of disease; ORR: overall response rate.

sis, digestive tract reaction and hepatic impairment. The definition and grading (grade 0-IV) of adverse events were based on the WHO standard of acute and subacute toxicity of antineoplastic agents [8]. For neutropenia, grade I is $1.5-1.9 \times 10^9/L$, grade II $1.0-1.4 \times 10^9/L$, grade III $0.5-0.9 \times 10^9/L$, and grade IV $<0.5 \times 10^9/L$; for reduced platelet count, grade I is $50-100 \times 10^9/L$, grade II $30-50 \times 10^9/L$, grade III $20-30 \times 10^9/L$, and grade IV $<10 \times 10^9/L$. Evaluation of thrombosis combined subjective sensation, including soreness, swelling pain as well as local skin redness, swelling, warm to touch, and pain at the site of limbs, armpit, shoulder and arm where indwelling catheter was placed, with color Doppler ultrasound examination. Digestive tract reaction is defined as one of the symptoms of nausea, vomiting, abdominal pain and diarrhea. Hepatic impairment is defined as an increase either in aminotransferases or in bilirubin.

With a follow-up of 3 years, the 1-, 2-, and 3-year progression-free survival (PFS) and overall progression-free survival (PFS), as well as the 1-, 2-, and 3-year survival and overall survival were compared between the groups.

Statistical analysis

All data were process using the SPSS 24.0 software package. Measurement data were ex-

pressed as mean \pm SD. Comparison between the two groups was based on t-test. Enumeration data were expressed as cases (%) or cases, and were compared using chi-squared test. The overall PFS and survival were presented with Kaplan-Meier estimator and were compared between the two groups using log-rank test. A P value of <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

No significant differences were observed for the control group vs. the observation group in sex, age, time to progression (time from last drug use to disease progression), tumor grading, or the last treatment cycle (all $P>0.05$). See **Table 1**.

Comparison of efficacy of chemotherapy

The ORR was higher in the observation group (83.33%) than that in the control group (66.67%) ($P<0.05$). See **Table 2**.

Comparison of incidences of adverse events

No significant differences were observed for the control group vs. the observation group in incidences of adverse events such as neutro-

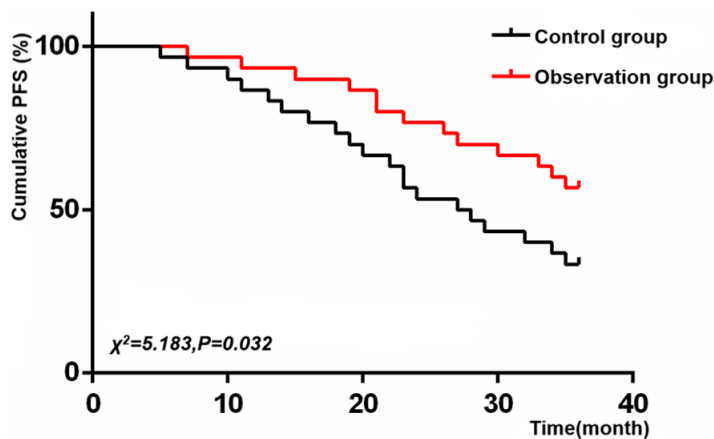
Table 3. Comparison of incidences of adverse events (n, %)

	The control group (n=30)	The observation group (n=30)	χ^2	P
Grade III/IV neutropenia	7 (23.33)	6 (20.00)	0.600	0.438
Grade III/IV thrombocytopenia	4 (13.33)	7 (23.33)	1.200	0.273
Rash	10 (33.33)	12 (40.00)	0.073	0.787
Thrombosis	7 (23.33)	9 (30.00)	0.073	0.787
Digestive tract reaction	5 (16.67)	7 (23.33)	0.089	0.766
Hepatic impairment	4 (13.33)	6 (20.00)	0.111	0.379

Table 4. Comparison of 1-, 2-, 3-year PFS (n, %)

	1-year PFS	2-year PFS	3-year PFS
The control group (n=30)	26 (86.67)	17 (56.67)	10 (33.33)
The observation group (n=30)	28 (93.33)	23 (76.67)	17 (56.67)
χ^2	0.741	5.279	4.986
P	0.389	0.031	0.035

PFS: progression-free survival.


Figure 1. Kaplan-Meier curves of overall progression-free survival.

penia, reduced platelet count, rash, thrombosis, digestive tract reaction and hepatic impairment (all $P>0.05$). See **Table 3**.

Comparison of 1-, 2-, 3-year PFS and overall PFS

No significant difference was observed between the two groups in 1-year PFS ($P>0.05$). The 2- and 3-year PFS in the observation group were significantly higher than those in the control group (both $P<0.05$). See **Table 4**.

A Kaplan-Meier curve was plotted according to the PFS and log-rank test was performed. Results showed that the overall PFS was better in the observation group than that in the control group ($P<0.05$). See **Figure 1**.

1-, 2-, and 3-year survival and overall survival

No significant difference was observed between the two groups in 1-year survival ($P>0.05$). The 2- and 3-year survival in the observation group were significantly higher than those in the control group (both $P<0.05$). See **Table 5**.

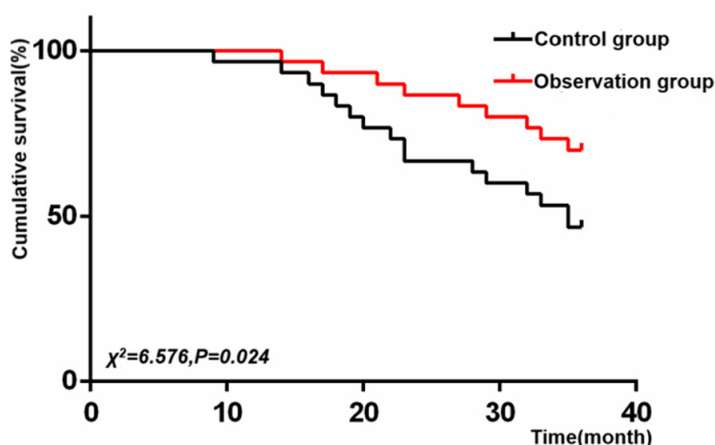
A Kaplan-Meier curve was plotted according to the survival period and log-rank test was performed. Results showed that the overall survival was better in the observation group than that in the control group ($P<0.05$). See **Figure 2**.

Discussion

FL is a common, indolent of NHL that derives from germinal center B cells, making it a B-cell lymphoma. The lymphoma consists of follicular center cells and different proportions of centroblasts. Also known as small cleaved cells, follicular center cells (FCCs) are characterized by diverse morphology with gyriform-like nuclear clefts often observed and nucleoli rarely seen. Centroblasts, also called non-cleaved cells, are large cells with round or lobular nuclei, fine chromatin, 1 to 3 nuclei, and slightly basophilic cytoplasm. A pathology study demonstrated that different proportions of FCCs and centroblasts will determine tumor typing, degree of malignancy and quality of prognosis [9]. Grading of FL is generally based on the amount of FCCs per high-power field: grade 1 is defined as 1-5 centroblasts per high-power field; grade 2, 6-15 centroblasts per high-power field; grade 3 (including grade 3a and 3b), >15 centroblasts per high-power field. A higher grading indicates a greater malignancy.

Table 5. Comparison of 1-, 2-, 3-year survival (n, %)

	1-year survival	2-year survival	3-year survival
The control group (n=30)	29 (96.67)	19 (63.33)	14 (46.67)
The observation group (n=30)	30 (100.00)	26 (86.67)	20 (66.67)
χ^2	1.017	6.830	5.407
P	0.313	0.021	0.030

**Figure 2.** Kaplan-Meier curves of overall survival.

cy. Clinically, FL grade 3b is comparable to diffuse large B-cell lymphoma in terms of malignancy and treatment [10]. FL mainly manifests as painless lymph nodes, which allows clear-cut diagnosis. Moreover, FL is sensitive to chemoradiotherapy. Treatment-naïve patients can mostly be cured by chemotherapy at early an stage with median survival of more than 5 years. However, a study found that although FL often has t (14;18) and high expression of BCL-2 protein, differences in morphology, clinical features and immunophenotypes, it would result in considerable differences in response to chemoradiotherapy and prognosis [11]. CHOP chemotherapy regimen is the first-line therapy of FL [12]. However, FL is prone to slow progression and recurrence, and most patients are at an advanced stage of FL when they are admitted to the hospital. All this could easily cause recurrence after initial treatment. Although clinical symptoms can be relieved to different extents after treatment; relapse in the short term leads to unsatisfactory long-term efficacy. A study confirmed that recurrent FL causes progression of disease and the shortening of the time interval between recurrences, resulting in a negative feedback loop [13]. Moreover, patients still have high rates of recurrence in the short term after induction chemo-

therapy; worsening the quality of prognosis and resulting in death due to a series of chemotherapy-induced complications [13]. At present, there is no standard for the treatment of recurrent FL, and salvage therapy is affected by a host of factors. Treatment of FL is an intractable problem for the department of hematology.

Rituximab, a human-mouse chimeric anti-CD20 monoclonal antibody, is a targeted cancer drug that specifically and directly induces the apoptosis of lymphoma cells derived from B lymphocytes. In addition, pharmacological studies have demonstrated that rituximab identifies CD20-positive B lymphoma cells and combines with CD20, while the other end of the antibody combines with phagocytes or killer cells to mediate

immune lysis of lymphoma cells and to induce complement-mediated cell lysis in lymphoma cells [14]. These mechanisms allow rituximab to effectively eliminate BCL-2 positive cells but have little cytotoxicity on normal cells. An *in vitro* study also found that rituximab is currently an ideal targeted therapy drug for recurrent/refractory FL as it improves the sensitivity of FL to chemotherapy drugs [15]. The study by Wenger et al. found that the ORR was 50.0-60.0% in patients with recurrent/refractory FL when treated with rituximab alone and was 60.0-70.0% in treatment-naïve patients, and by combining rituximab with CHOP, FMD, CVP or other chemoradiotherapy regimens, the survival could be prolonged and the ORR could be raised to 60.0-80.0% in patients with recurrent/refractory FL and to 80.0-95.0% in treatment-naïve patients [16].

Lenalidomide, a thalidomide derivative, is a novel immunoregulatory drug that can inhibit tumor angiogenesis and activity. It is considered as an ideal targeted cancer drug for fatal blood diseases, multiple myelomas and solid tumors [17]. The mechanism of action of lenalidomide remains unclear. Many studies revealed that lenalidomide plays its anti-cancer role in several ways, including: (1) inhibiting the

expression of intercellular adhesion molecules to reduce cell-matrix adhesion, (2) suppressing tumor angiogenesis by inhibiting the expression of vascular endothelial growth factors and fibroblast growth factors, (3) reducing the expression of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and other cytokines produced by immune cells including monocytes to interrupt cytokine-mediated proliferation, growth, drug resistance, and angiogenesis of tumor cells, (4) promoting the expression of interleukin-2 (IL-2) and interferon- γ (IFN γ), and enhancing the effect of cytotoxicity of natural killer (NK) cells, (5) regulating the immune system tumor microenvironment, inhibiting osteoclast activation, inducing tumor cell apoptosis, protecting normal B-cells and promoting the recovery of bone marrow hematopoiesis [18-20].

Combined use of rituximab and lenalidomide for FL patients can enhance the anti-cancer role of rituximab by regulating genes, and can also increase cytotoxicity of antibody-dependent cell-mediated cytotoxicity, lowering the risk of rituximab resistance and producing good synergistic efficacy. GS Nowakowski et al. found that the ORR was 98.0% for patients with diffuse large B-cell lymphoma who received the first-line therapy of lenalidomide 15 mg/d + rituximab 375 mg/m² (R2 regimen) combined with CHOP chemotherapy regimen; moreover, the therapy could overcome the prognostic impact of non-germinal center B-cell-like subtype on diffuse large B-cell lymphomas and would not be affected by other factors including age, bone marrow invasion, and large masses [21]. Several clinical studies have found that the R2 regimen has good efficacy as a first-line or second-line therapy for B-NHL, becoming a new option for those elderly or recurrent/refractory B-NHL patients who cannot receive high-intensity chemotherapy. In this study, we used combined therapy of rituximab and lenalidomide for patients with recurrent FL. The results showed that the ORR of the observation group (83.33%) was significantly higher than that of the control group (66.67%); moreover, a follow-up of 3 years after treatment showed that the 2- and 3-year PFS and survival were significantly higher in the observation group than those in the control group, indicating that combined therapy of rituximab and lenalidomide significantly improves efficacy of chemotherapy for

recurrent FL in the short term, better prevents the progression of disease and prolongs the survival of patients, which were consistent with the findings of previous studies.

Drug toxicity is an important criterion for evaluating anticancer drugs. The main drug toxicities of lenalidomide are myelosuppression, thrombosis and rash. Witzig et al. found that the main drug toxicities of lenalidomide in patients with recurrent/refractory FL were neutropenia and thrombocytopenia, and the incidences of grade IV neutropenia and thrombocytopenia were 17.0% and 6.0%, respectively [23]. J Ruan et al. found that the most common adverse effects of combined therapy of rituximab and lenalidomide for treatment-naïve patients with mantle cell lymphoma were rash (29.0%), thrombocytopenia (13.0%), inflammatory response syndrome (11.0%), fatigue (8.0%) [24]. The results of this study showed that no significant differences were observed between the two groups in the incidences of drug toxicities, of which the common drug toxicities were grade I/II myelosuppression (neutropenia, thrombocytopenia), rash and thrombosis, which were consistent with the findings of previous studies. However, some studies reported that though long-term maintenance therapy with rituximab improves short-term efficacy of chemotherapy, there is no evidence that the therapy benefits the long-term overall survival, and instead, the therapy may increase the risk of drug toxicity [25]. The results of this study demonstrated that combined therapy of rituximab and lenalidomide prolongs PFS and overall survival instead of increasing drug toxicity. Due to the limited sample size, certain bias is introduced in the results of this study, and larger sample size is warranted for future studies.

In conclusion, combined therapy of rituximab and lenalidomide for patients with recurrent FL can not only improve short-term clinical benefit rate, but also effectively controls the progression of disease, prolongs the survival period of patients, and offers good safety. This therapy can be a new option of treatment for recurrent FL.

Disclosure of conflict of interest

None.

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