Risk of Second Primary Cancer in Patients with B-cell Non-Hodgkin Lymphoma Receiving Rituximab-containing Chemotherapy: A Nationwide Population-based Study

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Abstract. *Aim: This study aimed to evaluate the risk of second primary cancer (SPC) in patients receiving rituximab-containing chemotherapy. Patients and Methods: A nationwide, population-based study was conducted using the National Health Insurance Database of Taiwan. Propensity score matching was performed to correct sample selection bias and logistic regression analysis was used to calculate odds ratios. Results: Patients receiving rituximab-containing chemotherapy or conventional chemotherapy were enrolled. After adjustment by propensity score matching, there were 1,607 patients in each group. SPC was noted in 11 patients (0.68%) with rituximab-containing chemotherapy and in 19 patients (1.18%) with conventional chemotherapy (p=0.142). There was no significant difference in the age distribution at onset of SPC (p=0.327). Multivariate logistic regression analysis revealed rituximab-containing chemotherapy was not associated with risk of SPC (odds ratio (OR)=0.58; 95% confidence interval (CI)=0.28-1.23; p=0.157). Conclusion: Incorporation of rituximab into conventional anti-lymphoma chemotherapy did not increase the risk of SPC in patients with B-cell non-Hodgkin lymphoma (NHL).*

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy in adults with a significantly increased incidence worldwide in recent decades (1-4). In Taiwan, the annual report of cancer registration of 2007 revealed that NHL was the twelfth leading site of new cancer cases among men and women accounting for around 2% of new cancer cases. In addition, NHL was ranked ninth in men and tenth in women for cancer-related mortality accounting for around 2.4% of mortality cases.

The long-term survival of NHL patients has significantly improved in recent years possibly due to advances in diagnostic tools and supportive care, as well as the development of more effective chemotherapeutic agents. Among the patients with B-cell NHL, and especially follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), the introduction of the anti-CD20 monoclonal antibody rituximab was an important milestone in treatment. Rituximab is a chimeric monoclonal antibody targeting the CD20 antigen, which is expressed on more than 90% of B-cell lymphoma cells (5). The combination of rituximab and conventional chemotherapy has significantly improved the prognosis of patients with DLBCL and FL, while current studies have shown that it is generally safe for short-term treatment (6-10).

Since more patients with B-cell lymphoma survive after treatment, the long-term effects of lymphoma treatment are emerging as an important issue for these survivors. Since CD20 is expressed in both normal and malignant B lymphocytes, rituximab may further suppress the lymphoid system leading to increased risk of infectious diseases, such as re-activation of hepatitis B or herpes infection (11-13). Another important issue is whether an impaired immune system increases the risk of second primary cancer (SPC). In the pre-rituximab era, the incidence rate of SPC in patients with NHL was ranging from 1 to 8 percent (14-16). In the rituximab era, a phase III clinical trial comparing the treatment outcome between rituximab-containing chemotherapy and conventional chemotherapy in young patients with DLBCL revealed a similar incidence rate

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of SPC (9). However, related data about the impact of rituximab on the incidence of SPC in Asian patients with B-cell NHL are lacking and, thus, it is not possible to initiate a clinical trial to elucidate this issue.

We, therefore, conducted this population-based study to investigate whether the incorporation of rituximab into conventional chemotherapy as a front-line therapy would increase the risk of SPC in patients with B-cell NHL. The analysis included comparisons of the incidence and pattern of SPC between patients receiving chemotherapy with or without rituximab.

Materials and Methods

National Health Insurance Research Database. We conducted this nationwide cohort using data from all patients diagnosed with NHL in the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance (NHI) program was implemented in Taiwan on March 1st of 1995 to provide compulsory universal health insurance to all citizens. The coverage rate was 96% of the whole population in 2000, rising to 99.6% in 2012. The coverage provides inpatient care, outpatient services, childbirth, dental care, Chinese medicine, physical therapy, preventive medicine, home care and rehabilitation for chronic mental illnesses. The NHI medical claims database includes ambulatory care, hospital inpatient care, dental services and prescription drugs; the NHIRD is the most comprehensive nationwide population-based dataset in Taiwan.

The NHI uses a registry system for catastrophic illnesses, including chronic mental illness, autoimmune diseases, end-stage renal disease and malignant diseases. All patients who meet the criteria are registered as having a catastrophic illness and these patients do not have to pay co-payments and, in addition, their data records are very comprehensive. For patients with NHL, catastrophic illness certificates are issued once lymphoma is proven by pathology.

This study cohort included patients with NHL over a 7-year period, from January 1, 2002, to December 31, 2008, because rituximab was approved by the NHI in 2002 for the treatment of DLBCL and FL, the two most common subtypes of NHL. The patients with NHL were included if they were aged 20 years and older, had a first diagnosis of NHL (International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes 200.0-200.8 and 202.0-202.9) with no previous diagnosis of cancer. Patients with HIV infection (code 042) before the diagnosis of NHL were excluded. To assure the completeness and accuracy of ICD-9-CM coding, the included patients were validated by registration of catastrophic illness. All included patients were tracked until death or the end of 2008.

For the purpose of this study, we analyzed patients with NHL who received first-line treatment with or without rituximab. Patients who received chemotherapy only were classified as the control group. In terms of first-line chemotherapy regimen, the patients in the rituximab-containing chemotherapy group were those who received a complete course of rituximab-containing chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or R-CEOP (rituximab, cyclophosphamide, epirubicin, vincristine, prednisolone). Control group patients were those who received a complete course of conventional chemotherapy with CHOP or CEOP. To eliminate the effects of other chemotherapeutic agents, patients who received combined chemotherapy other than CHOP/CEOP or R-CHOP/R-CEOP were excluded. Patients who received radiotherapy for bulky disease were also enrolled for analysis.

SPC was defined as any site of second malignancy either *in situ* or invasive, except for Kaposi's sarcoma in HIV-positive individuals, diagnosed at least 6 complete months after the diagnosis of lymphoma but before death. Any cases of SPC diagnosed in patients who received initial treatment for lymphoma at other medical centers were excluded, as were all malignancies diagnosed within 6 months of the diagnosis of lymphoma and also cases of third primary malignancies.

This study also evaluated the comorbidities of the enrolled patients using the Charlson comorbidity index (CCI). The index was calculated to define the existing comorbidities using all diagnosis codes for the year prior to the index date for all inpatients and outpatients. The CCI was defined by Charlson *et al*. (17) and the Deyo-Charlson comorbidity index and is based on ICD-9-CM codes in claims data. It has been widely used to analyze the impact of comorbidities on mortality (17, 18). The patients were categorized into two groups based on CCI scores of 0 and ≥1.

The NHIRD provided by the official NHI program contains totally de-identified and encrypted data to protect the privacy of the patients, thus the study was exempt from full review by the Institutional Review Board of Kaohsiung Medical University. The study also conformed to the criteria of the Department of Health, Taiwan, for the exemption of institutional review board review and requiring informed consent.

Statistical analysis. Propensity score matching was performed to correct sample selection bias. The frequency between each categorical variable was compared by the chi-square test (χ^2 test), while the independent two samples *t*-test was used to compare continuous variables. Relative risk analysis was performed by calculating the odds ratio (OR) and 95% confidence interval (CI) using multivariate logistic regression.

All statistical analyses were based on two-sided hypothesis tests with a significance level of $p<0.05$. The analyses were performed using the SPSS, version 17.0 (SPSS, Chicago, IL, USA).

Results

From 2002 to 2008, 8,403 patients with NHL were identified, including 4,089 who received R-CHOP/R-CEOP or CHOP/CEOP as first-line chemotherapy. With a follow-up period of 9,710 person-years, SPC was found in 39 patients (0.95%). After adjusting for age, gender, CCI, radiotherapy and chemotherapeutic agents by propensity score matching, a total of 3,214 patients were included with 1,607 patients in each group (Figure 1). Out of these 3,214 patients, 30 (0.93%), with a mean age of 55.4 years, developed SPC. In the rituximab-containing chemotherapy group, the patients were diagnosed with NHL at a mean age of 57.7 years and SPC at a mean age of 55.4 years. In the control group, the patients were diagnosed with NHL at a mean age of 57.6 years and SPC at a mean age of 55.3 years. The duration

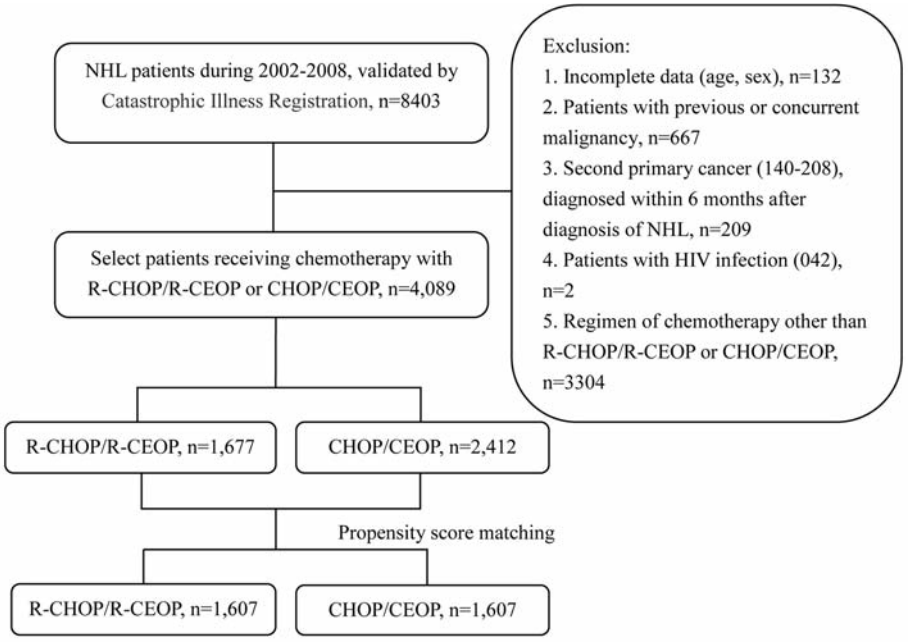

Figure 1. *Flow chart summarizing the study cohort. NHL, Non-Hodgkin lymphoma; HIV, human immunodeficiency virus; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.*

from diagnosis of NHL to SPC ranged from 6.1 to 67.2 months in the control group and 6.3 to 71.4 months in the rituximab-containing chemotherapy group. With respect to incidence of SPC in each group, there were 11 (0.68%) in the rituximab-containing chemotherapy group (R-CHOP/R-CEOP, n=1607) and 19 (1.18%) in the control group (CHOP/CEOP, n=1607). There was no significant difference in incidence rate between both groups (p=0.142) (Table I).

The sites of the 30 cases of SPC are listed in Table II. Among these 30 patients, 4 (13.33%) had hematological malignancies, including 2 in the rituximab-containing chemotherapy group and 2 in the control group.

With respect to age at the diagnosis of SPC, there were 8, 6 and 5 patients at the age of fifty or less, fifty-one to sixty-four and more than sixty-five, respectively, in the control group. In the rituximab-containing chemotherapy group, there were 5, 2 and 4 patients at the age of fifty or less, fifty-one to sixty-four and more than sixty-five, respectively. No significant difference was noted in age at the onset of SPC between the two groups (p=0.327).

The annual incidence rate of SPC was also evaluated in the two groups. The development of SPC occurred mainly in the first three years after the diagnosis of NHL in both groups, including 8 patients (72.73%) in the rituximab-containing chemotherapy group and 16 patients (84.21%) in the control group (Figure 2). The cumulative incidence reached a plateau in the third year after the diagnosis of NHL (Figure 3). Multivariate logistic regression for the relative risk of SPC revealed that the incorporation of rituximab was not associated with a higher incidence of SPC (OR, 0.58; 95% CI, 0.28-1.23; p=0.157) (Table III).

Discussion

In the present study, we compared the incidence of SPC in patients with B-cell NHL receiving rituximab-containing chemotherapy (R-CHOP/R-CEOP) with patients receiving conventional CHOP/CEOP chemotherapy. The results revealed that patients with B-cell NHL did not have a higher risk of SPC after receiving rituximab-containing chemotherapy.

The administration of rituximab causes B-cell depletion and has been found to have an effect on cellular and humoral immunity (19); however, an association between B-cell depletion and the development of subsequent malignancy has yet to be elucidated. Some mechanisms may support the results of our study. First, rituximab has been reported to cause the rapid depletion of CD20-expressing B cells by antibody-dependent cell-mediated cytotoxicity (20, 21). During B lymphocyte differentiation, CD20 is not expressed in progenitor and precursor B cells until immunoglobulin light chain rearrangement and, therefore, CD20 is expressed in only a small fraction of B lymphocytes, such as mature B cells and most malignant B cells (22). Second, a previous

Table I. *Characteristics of the cohort and incidence of SPC before and after propensity score matching.*

	Unmatched							Matched						
	R-CHOP/R-CEOP (n=1,677)			CHOP/CEOP (n=2,412)				R-CHOP/R-CEOP (n=1,607)			CHOP/CEOP (n=1,607)			
	No. of patients	Person-years of follow-up	%	No. of patients	Person-years of follow-up	%	*p*-Value	No. of patients	Person-years of follow-up	%	No. of patients	Person-years of follow-up	%	*p*-Value
Gender							0.008							0.393
Female	764	1,409	45.57	998	2,952	41.37		715	1,343	44.49	691	2,008	42.99	
Male	913	1,681	54.43	1,414	3,668	58.63		892	1,650	55.51	916	2,293	57.01	
Age							<0.001							0.993
≤50	517	915	30.83	1,094	3,409	45.36		513	911	31.92	516	1,672	32.11	
51-64	546	1,021	32.56	693	1,856	28.73		504	959	31.36	503	1,372	31.30	
≥65	614	1,155	36.61	625	1,355	25.91		590	1,123	36.72	588	1257	36.69	
CCI							<0.001							1.000
0	1,613	3,044	96.19	2,366	6,538	98.09	0.004	1,565	2,969	97.39	1,565	4,230	97.39	
≥1	64	46	3.81	46	82	1.91		42	24	2.61	42	70	2.61	
RT														0.086
With	416	745	24.81	698	1,530	28.94		405	726	25.20	448	971	27.88	
Without	1,261	2,346	75.19	1,714	5,089	71.06		1,202	2,267	74.80	1,159	3,330	72.12	
SPC							0.191							0.142
No	1,665	3,044	99.28	2,385	6,510	98.88		1,596	2,949	99.32	1,588	4,221	98.82	
Yes	12	47	0.72	27	110	1.12		11	44	0.68	19	80	1.18	

SPC, Second primary cancer; CCI, Charlson comorbidity index; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.

study showed that the recovery of the normal B-cell population occurs 6 to 9 months after discontinuation of rituximab (23). In addition, several mouse model studies have reported that the depletion of B cells by anti-CD20 antibodies may augment the anticancer effect of the immune system (24, 25). Based on these mechanisms, the effect of rituximab on immune function appears to be minimal and the risk of cancer development low.

In the present study, we performed propensity matching to correct for the bias of sample selection and to minimize the potential bias of the histological subtype. The histological subtypes of the patients who received rituximab-containing chemotherapy included DLBCL and FL; however, the histological subtypes of the patients in the control group may have included a small portion of other lymphomas, such as T-cell lymphoma other than DLBCL or FL. The most ideal way to eliminate this effect of heterogeneity of histological subtype would be to initiate a clinical trial; however, this may not be possible in real-world clinical practice since rituximab-containing chemotherapy has become the standard treatment for B-cell NHL. In addition, we only enrolled and analyzed patients who received conventional CHOP/CEOP chemotherapy or R-CHOP/R-CEOP chemotherapy as first-line treatment. The patients who received first-line COP or R-COP were not enrolled to eliminate the effect of anthracycline.

Table II. *Distribution of SPC in the patients receiving R-CHOP/R-CEOP or CHOP/CEOP.*

	All patients (n=3,214)	R-CHOP/R-CEOP (n=1,607)	CHOP/CEOP (n=1,607)
All SPCs	30 (0.93%)	11 (0.34%)	19 (0.59%)
Sites of SPC			
Head and neck (Mouth, tongue, pharynx, larynx)	3	1	2
Digestive system	4	1	3
Lung and mediastinum	1	1	0
Prostate	4	1	3
Thyroid	4	2	2
Soft tissue	1	0	1
Hematologic malignancy	4	2	2
All others	9	3	6

SPC, Second primary cancer; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.

The present study has several strengths. First, the NHIRD includes a large number of patients without selection bias because more than 99% of the patients who met the study criteria were included in the database. Second, the NHIRD is

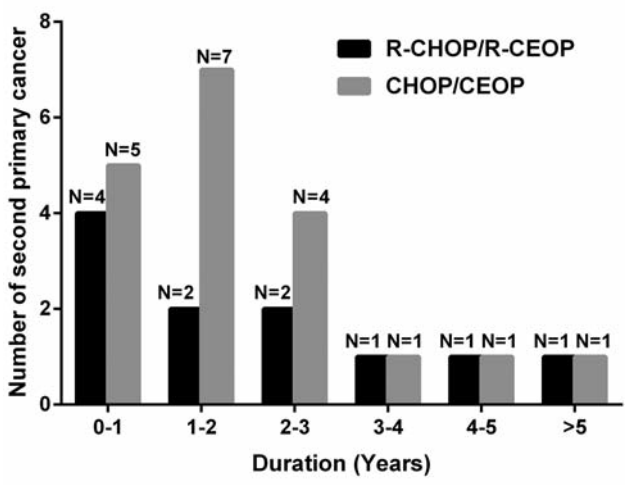

Figure 2. *The annual number of cases of second primary cancer in patients with NHL receiving R-CHOP/R-CEOP or CHOP/CEOP. R, Rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.*

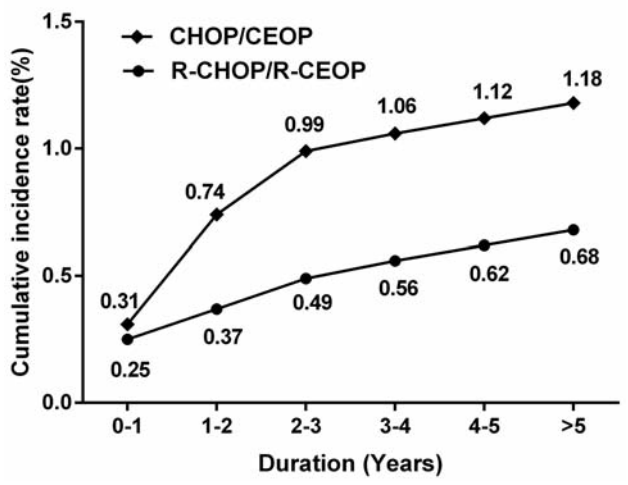

Figure 3. *The cumulative incidence rate (CIR) of second primary cancer in patients with NHL receiving R-CHOP/R-CEOP or CHOP/CEOP. R, Rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.*

Table III. *Multivariate logistic regression to analyze the risk of second primary cancer.*

Variable	Number	Number of SPC (%)	OR (95% CI)	*p*-Value
Gender				
Female	1406	13 (0.92)	Reference	
Male	1808	17 (0.90)	1.04 (0.50-2.14)	0.926
Age (years)				
≤50	1029	13 (1.26)	Reference	
51-64	1007	8 (0.79)	0.65 (0.27-1.59)	0.349
≥65	1178	9 (0.76)	0.63 (0.27-1.50)	0.297
CCI				
0	3130	30 (0.96)	Reference	
≥1	84	0 (0.0)	0.00 (0.00)	0.997
Radiotherapy				
With	853	11 (1.29)	Reference	
Without	2361	19 (0.80)	0.66 (0.31-1.41)	0.285
Regiment				
CHOP/CEOP	1607	19 (1.18)	Reference	
R-CHOP/R-CEOP	1607	11 (0.68)	0.58 (0.28-1.23)	0.157

CCI, Charlson comorbilty index; OR, odds ratio; 95% CI, 95% confidence interval; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone.

comprehensive and it is unlikely there were missing data of medical procedures or drug administration. However, some limitations should be noted. First, detailed information with regards to definite histological subtype, clinical stage and dosage of chemotherapeutic agents were unavailable in the NHIRD. In addition, as mentioned above, the histological subtype of the patients in the control group was more heterogeneous than in the rituximab-containing chemotherapy group. Second, the duration of follow-up in both groups may be relatively short. However, the cumulative incidence rate of SPC reached a plateau in the first 3 years and, thus, the results of a longer follow-up duration may be similar.

In conclusion, the present study revealed that the incorporation of rituximab into conventional chemotherapy was not associated with higher risk of SPC. In addition, rituximab had no obvious effect on the age at onset and cumulative incidence rate of SPC in patients with NHL.

Conflict of Interests

The Authors have no competing interests.

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