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Incidence Patterns of Sequential or Composite Lymphoma: A Population-Based Cancer Registry Study

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The development of multiple histologic types of lymphoma in a single patient has been sporadically reported as sequential or composite lymphoma. However, the incidence pattern of such patients has been rarely evaluated in a large population-based setting. We investigated the incidence of sequential or composite lymphoma based on 11,174 lymphoma records from a population-based cancer registry between 1985-2012 in Nagasaki Prefecture, Japan. We identified 99 lymphoma records were of 49 independent patients other than relapse. The prevalence of the sequential or composite lymphomas in a single patient was 0.44% (95% confidence interval [95% CI], 0.32-0.56%) without sex difference. Among the 49 patients, five (10.2%) were composite/discordant lymphoma. The most frequent "composite lymphoma" was a combination of diffuse large B-cell lymphomas (DLBCL) and adult T-cell leukemia (n = 3). A case of "discordant lymphoma" was a combination of follicular lymphoma on spleen and Waldenström macroglobulinemia on bone marrow. The rest of the patients (n = 44, 89.8% of all composite lymphoma) were "sequential lymphoma" with various combination of lymphoma subtypes on different dates. The major combination of the sequential lymphoma was DLBCL after marginal zone lymphomas (n = 4). In the era of improved survival of lymphoma patients, hematologists should be aware of the development of additional lymphomas.

Keywords: cancer registry; composite lymphoma; discordant lymphoma; epidemiology; sequential lymphoma
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Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous neoplasm with a wide range of etiological factors and pathological patterns including diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), follicular lymphoma (FL), marginal zone lymphoma (MZL), mucosa-associated lymphoid tissue (MALT) lymphoma, Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL), Adult T-cell leukemia/lymphoma (ATL), and other miscellaneous types of lymphoma (Swerdlow et al. 2016). Recent global-epidemiological reports on NHL have shown that the temporal trend in the incidence rate of NHL was stable or decreasing in the majority of countries (Miranda-Filho et al. 2019), and that the prognosis of NHL has improved due to the effectiveness of the combination chemotherapy and a variety of molecular targeted agents (Armitage et al. 2017).

However, as the overall prognosis of patients with NHL has improved, the occurrence of multiple distinctive histologic types of lymphoma in a single patient has become noticeable recently. Such patients developing subsequent different histological types of lymphomas are known to be diagnosed as sequential lymphoma (Siebert et al. 1999), discordant lymphoma (Acker et al. 1983), or

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transformed lymphoma (Al-Mansour et al. 2010). Furthermore, patients of more than one histological type of lymphoma simultaneously in a single tissue are known as composite lymphoma (Kim 1993). However, the incidence rate and the combination pattern of sequential or composite lymphomas that developed in a patient have been rarely evaluated in a large-scale population-based setting.

Therefore, we aimed to assess the frequency, the incidence pattern, and the prognosis of patients having multiple distinctive histologic subtypes of lymphoma in a large population-based cancer registry.

Materials and Methods

Study design and data sources

This was a retrospective observational study examining the prevalence and the combination patterns of "patients with multiple distinctive histologic subtypes of lymphoma" and the clinical characteristics based on data from the Nagasaki Prefectural Cancer Registry (NPCR) in Japan. The NPCR was established in 1974, covering a population of approximately 1.56 million people in the catchment areas, and is known to be one of the highest quality cancer registries (the death certification is only 9% and the proportion of morphological verification is 79%) (Forman et al. 2014). In the NPCR, three pathologists regularly reviewed the pathology sheets and smears of the registered data, and dates of death have been regularly updated based on the official death certification. Unfortunately, information on causes of death were not fully available from the NPCR. The annual incidence rate of lymphoma in the NPCR has been regularly published in Japanese, and in English by the International Agency for Research on Cancer (Bray et al. 2017). The annual crude incidence of any lymphomas in the NPCR during 2008-2012 was reported to be 20.5 for men and 17.2 for women per 100,000 people (Bray et al. 2017). The present study was approved by the institutional review boards of both the NPCR (approval no. 28-337) and the Nagasaki University (approval no. 16060290).

Dataset assembly

We obtained a dataset of 12,645 patients with lymphoma in the NPCR as of 2012 that was coded based on the International Classification of Diseases for Oncology (ICD-O) system. Cases coded based on the ICD-O-1 and 2 systems were converted to the ICD-O-3 system by pathologists in this study (D.N., L.T.M.H. and S.M.). For cases coded with uncertain ICD-O codes, pathologists in this study anonymously reviewed the cancer registry sheets or pathological reports with permission from the NPCR as much as possible.

From the 12,645 crude records of patients with lymphoma, we first excluded 1,465 records because the year of diagnosis was before 1985 (n = 123) or the ICD-O codes were other than lymphoma (n = 1,342). We then specified a total of 11,180 records that were diagnosed in 1985-2012; from which we further excluded 11,069 records because there was only a single record for each patient. The remaining 111 lymphoma records were of 55 patients. After reviewing these 111 records, we identified 12 records were of six relapsed patients which were therefore unified as six patients. Finally, we determined that 99 records of lymphoid malignancy were of 49 independent patients (Fig. 1).

From the crude dataset of 99 records of 49 independent patients with lymphoid malignancy, we further identified individual cases having multiple records based on individual registry code and on date of diagnosis, and then classified the patients as follows; (1) a patient having sequential identical ICD-O-3 codes of lymphoma on different organs at different dates or years was treated as "relapse" of the first lymphoma; (2) a patient having multiple ICD-O-3 codes on the same or different tissue on identical diagnosis dates was treated as a "composite or discordant" case (Kim 1993); and (3) a patient having multiple ICD-O-3 codes on different diagnosis dates was treated as "sequential" case. We then included the patients of the group (2) and (3) in analyses for the age- and sex-specific frequencies of "cases of sequential or composite lymphoma".

Statistical analysis

The probability of overall survival (OS) was calculated

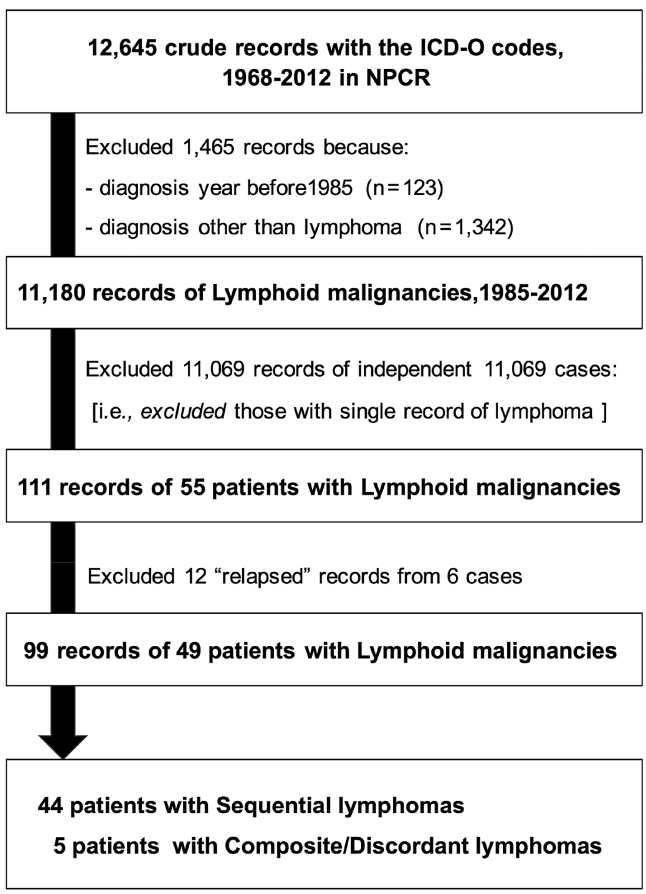

Fig. 1. Flow-chart of the study.
NPCR, Nagasaki Prefectural Cancer Registry.

from the date of pathologically confirmed first lymphoma to the date of death or the last follow-up period in the NPCR as of September 2016 by using GraphPad Prism 7 software (GraphPad Software, Inc., La Jolla, CA). All other statistical analyses were performed using JMP Pro 13.0.0 (SAS Institute, Cary, NC).

Results

The overall prevalence of the 49 patients with multiple lymphomas among all lymphoma patients was 0.44% (95% confidence interval [CI], 0.32-0.56%) for all, 0.50% (95% CI, 0.35-0.72%) for male, and 0.37% (95% CI, 0.20-0.54%) for female. The male-to-female odds ratio for the prevalence of multiple lymphomas was 1.35 (95% CI, 0.76-2.42, P = 0.29), which indicated that there was no statistically significant sex difference in the prevalence of multiple lymphomas. Among the 49 patients with multiple lymphomas, five (10.2%) were composite/discordant lymphomas (Table 1), of those, four were "composite lymphoma" (Kim 1993) with a combination of DLBCL and ATL or other T-cell lymphoma in a single tissue, and the rest one was "discordant lymphoma" (Acker et al. 1983) with a combination of FL in the spleen and Waldenström macroglobulinemia in the bone marrow. The remaining 44 patients (89.8%) were "sequential lymphoma" (Siebert et al. 1999) of various combinations of lymphoma types on different dates (Tables 2 and 3). The frequent combination of the first/second types of lymphoma were MZL/DLBCL (n = 4), DLBCL/ATL (n = 3), and WM or LPL/DLBCL (n = 3). The median age at diagnosis of all the first and second lymphomas was 65.2 years (ranges 26.6-90.5 years) and 73.3 years (ranges, 28.4-93.7 years), respectively (Fig. 2A, Table 2). The median interval between the first and the second lymphoma was 4.3 years (ranges, 0.1-22.2 years). Regarding cell-lineage, 19 (43.2%) had distinct cell-lineage types of lymphomas between the first and the second ones (Table 2). The OS of the 44 patients with sequential lymphoma was 22.5% (95% CI, 17.9-13.9%) as of September 2016 with the median survival time was 9.5 years (Fig. 2B).

Discussion

In the present study, the frequency of patients with multiple histological types of lymphoma among all patients with lymphoma was 0.44%, which was distinctively lower

Table 1. Summary of five patients with composite/discordant lymphomas.

Case	Sex	Age at Diagnosis	Date of Diagnosis	Tumor Site	Diagnosis	Type
1	Male	61.6 y	2008, Nov.	Colon	EBV-positive DLBCL + T-lymphoma	composite
2	Male	63.5 y	2011, Nov.	LN (pharynx)	DLBCL + ATL	composite
3	Male	72.1 y	2012, July	LN	DLBCL + ATL	composite
4	Female	67.9 y	2012, Oct.	LN	DLBCL + ATL	composite
5	Male	73.7 y	2009, Sep.	Spleen (FL) + Bone Marrow (WM)		discordant

ATL, Adult T-cell leukemia/lymphoma; EBV, Epstein-Barr virus; FL, Follicular lymphoma; DLBCL, Diffuse large B-cell lymphoma; LN, Lymph node; WM, Waldenström's macroglobulinemia.

Table 2. Summary of 44 patients with sequential lymphomas.

Characteristics		Summary Statistics
Sex	Male, No (%)	26 (59%)
	Female, No (%)	18 (41%)
Age at 1st lymphoma, years		
	Median (min, max), years	65.2 (26.6, 90.5)
Age at 2nd lymphoma, years		
	Median (min, max), years	73.3 (28.4, 93.7)
Interval between 1st and 2nd lymphomas		
	Median (min, max), years	4.3 (0.1, 22.2)
Cell-lineage combination of 1st and 2nd lymphoma		
	B → B	22 (50%)
	B → T	16 (36%)
	T → T	3 (7%)
	T → B	3 (7%)

B, B-cell, T, T-cell.

Table 3. Combination patterns of 44 patients with sequential lymphomas.

ICD-O-3 Morphology Codes Group		2nd Lymphoid malignancies																
		CLL /SLL	MCL	FL	DLBCL	MZL	B-PLL /HCL	MM	WM/LPL	B-NOS	Cutaneous T	ATL	AITL	ALCL	Other-T	Hodgkin	Unkown	Total
1st Lymphoid malignancies	CLL/SLL		1			2						1		1				5
	MCL																	0
	FL					1									1			2
	DLBCL										1	3	1		1			6
	MZL				4						1		1		2			8
	B-PLL/HCL	1																1
	MM				1					1		1						3
	WM/LPL				3												1	4
	B-NOS							2				1						3
	CutaneousT				1													1
	ATL							1										1
	AITL	1														1		2
	ALCL											1				1		2
	Other-T																	0
	HL				2	1						1						4
	Unkown							1		1								2
	Total	2	1	0	11	4	0	4	0	2	2	8	2	1	4	2	1	44

ATL, Adult T-cell leukmia/lymphoma; AITL, Angioimmunoblastic T-cell lymphoma; ALCL, Anaplastic large-cell lymphoma; B-NOS, B-cell not otherwise specified; B-PLL/HCL, B-cell prolymphocytic leukemia; CLL, Chronic lymphocytic leukemia; Cutaneous T, Cutaneous T-cell lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; HCL, Hairy cell leukemia; HL, Hodgkin's lymphoma; LPL, Lymphoplasmacytic lymphoma; MALT, Mucosa-associated lymphoid tissue lymphoma; MCL, Mantle cell lymphoma; MM, Multiple Myeloma; MZL, Marginal zone lymphoma; Other-T, Other T-cell lymphoma; SLL, Small lymphocytic leukemia; WM, Waldenström macroglobulinemia: ICD-O-3, International Classification of Diseases for Oncology 3rd Revision.

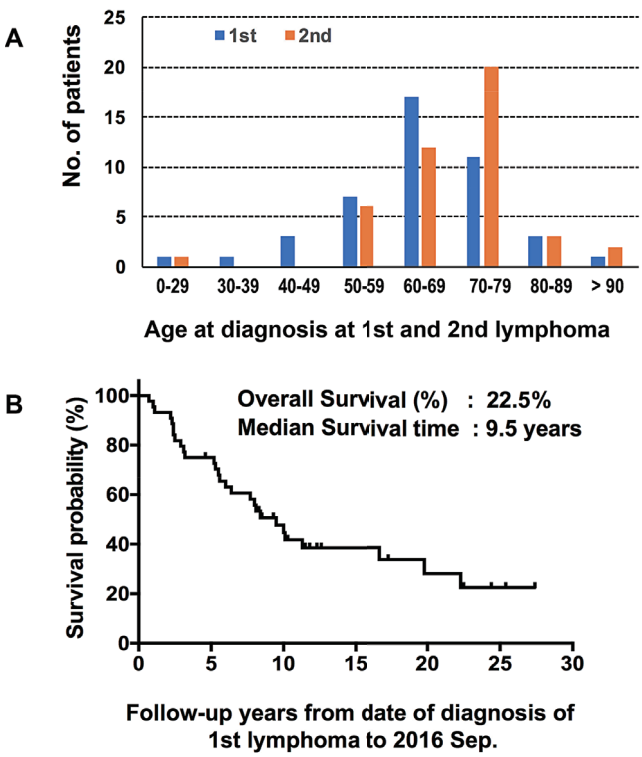

Fig. 2. Distribution of age at diagnosis of the first and second lymphomas, and overall survival in 44 patients with sequential lymphoma.
A: Distribution of age at diagnosis of the first and second lymphomas. B: Overall survival from the data of diagnosis of the first lymphomas.

than that in the US (4.7%) (Kim 1993), Italy (13%) (Tucci et al. 2005), Germany (0.9%) (Khristi et al. 2013), and France (12%) (Aussedat et al. 2020). The reasons for the lower frequency of multiple histological types of lymphoma in a patient in the present study are unknown, but a possible reason might be related to difference in study design, disease definition, and ethnicity of the study subjects. Additional well-designed epidemiological studies of sequential or composite lymphoma among other prefectural cancer registries and Asian population other than Japan are necessary to confirm the present study.

Furthermore, in the present study, the most frequent combination pattern of 1st and 2nd lymphomas were MZL and DLBCL, which have been well described in the literature as a pattern of the high-grade transformation of the low-grade lymphoma (Agbay et al. 2016). However, the most notable result in the present study was that ATL developed as the second most common lymphoma after any types of initial lymphoma (Table 3). In particular, there were three DLBCL/ATL composite lymphomas, of which combination pattern was extremely rare in the literature (Suefuji et al. 2012). This was primarily because Nagasaki prefecture, located in the southwest of Japan, is one of the well-known endemic regions for Human T-cell leukemia virus type 1 (HTLV-1) (Sagara et al. 2018). Even though the majority of the HTLV-1-infected individuals are asymptomatic and live longer free of HTLV-1-related symptoms and diseases, a part of them develop ATL, and another part of them become immunocompromised status due to the impaired CD4 T-cells similar to HIV-infected persons. All of these facts suggest that HTLV-1-infected individuals might be susceptible to develop any types of malignant lymphoma including ATL due to immunocompromised status similar to the development of HIV-related lymphoma among HIV-infected persons. Therefore, we recommend for clinicians to follow up carefully HTLV-1-positive NHL patients in terms of the development of ATL after treatment.

Although the present study was done by using a large-scaled population-based cancer registry data, there were several limitations such as a retrospective study design

based on cancer registry data, lack of clinical information of the registered ATL patients, and lack of information on comorbid diseases that affect the survival results. Therefore, to confirm results of the present study, additional large-scale population-based studies are required in both HTLV-1-endemic and non-endemic areas in Japan.

In conclusion, the present study shows for the first time the evidence of the incidence patterns of rare sequential or composite lymphoma in a large-scale population-based setting in Japan. In the era of improved survival of patients with lymphomas, clinicians should be aware of the potential development of secondary, or more, additional lymphoid malignancies after treatment for the first lymphoma.

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Author Contributions

M.I. designed the research plan and obtained data from the NCR after permission; L.T.M.H., D.N., S.M. and M.N. performed pathological confirmation; L.T.M.H., D.N. and M.I. analyzed the data; D.N. and M.I. drafted the manuscript. All authors critically reviewed and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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