Second Primary Malignancies in Mantle Cell Lymphoma: A U.S. Population-based Study

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Abstract. *Background/Aim: The risk of second primary malignancy (SPM) in mantle cell lymphoma (MCL) is not well-known. In this population-based study, we analyzed rates of SPM in adult patients with MCL. Patients and Methods: We selected adult (≥18 years) patients with MCL as first primary malignancy diagnosed during January 1992 to December 2011 from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 13 database. We used multiple standardized incidence ratio (MP-SIR) session of SEER* stat software to calculate the risk of second primary malignancies. Results: Among 3,149 patients, 261 (8.29%) developed 287 second primary malignancies with observed/expected (O/E) ratio of 1.32 (95% confidence interval (CI=1.17-1.48, p<0.001). The median time to SPM from the time of diagnosis was 47 months (range=6 months to 17.91 years). The significant excess risks were observed for skin, excluding basal and squamous cancer, (N=22, O/E=2.24, CI=1.4-3.39, p<0.001), thyroid malignancy (O/E=3, CI=1.1-6.52, p<0.01), acute myeloid leukemia (O/E=7.74, CI=4.54-13.94, p<0.001), chronic lymphocytic leukemia (O/E=7.27, CI=4.44-11.23, p<0.001) and Non-Hodgkin's lymphoma (NHL) (O/E=3.79, CI=2.64-5.27, p<0.001). The risk of malignancies of brain, thyroid, rectum and anal canal were higher within the first two years of diagnosis of MCL. Risk of skin cancer, excluding basal and squamous cancer, was higher after two years of latency. Conclusion: There is significantly higher risk of second primary malignancies in patients with mantle cell lymphoma compared to the general population. Patients may benefit from cancer-specific screening during follow-up.*

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Non-Hodgkin's lymphoma (NHL) is the 7th commonest malignancy among men and women (1). Improvements in diagnostics and therapeutics have led to improvement in long-term survival of patients with NHL (2-4). As a result of improvement in survival rates of lymphoma patients, prevalence of survivors is expected to increase. Mantle cell lymphoma (MCL) accounts for approximately 7% of adult NHLs in the United States and Europe, with an incidence of 4-8 cases per million persons per year (5-8). Recent advances in the diagnostics and therapeutic strategies have led to improvement in survival of MCL patients (9).

Long-term complications, including second primary malignancies (SPMs), are becoming important in lymphoma survivors. Previous studies have shown significantly increased SPMs in several hematological malignancies and solid tumors (10-13). Previous studies have also shown higher risk of SPMs in patients with NHL, which is a group of heterogeneous diseases with different biology and treatment. Thus, it is important to evaluate SPMs in specific NHLs.

Therefore, we analyzed the risk of SPM in adult patients with MCL from the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Result (SEER) database.

Patients and Methods

We selected adult patients (≥18 years) with MCL from National Cancer Institute's, Surveillance, Epidemiology and End Result 13 (SEER 13) Regs Research Data, Nov 2013 Sub (1992-2011), released in April 2014 (14). We included patients diagnosed from January 1992 to December 2011. We excluded patients who were diagnosed at autopsy or those with diagnosis on death certificate only. We excluded patients who were lost to follow-up after the diagnosis of MCL. Patients were followed up from diagnosis of MCL to the date of last known vital status, death or the last point of data collection. Using Warren and Gates criteria as modified by NCI, SPM was defined as metachronous malignancy developing ≥6 months after the index MCL (15-16).

We used the multiple primary standardized incidence ratio (MP-SIR) session of SEER*stat software, Version 8.1.5 March 31, 2014, to calculate the standardized incidence ratio (SIR), absolute excess risk (AER) and confidence interval (CI) for SPM. The expected

SPM was calculated for a reference SEER cohort of identical age, sex and time period.

The SIR is also known as relative risk. SIR is a relative measure of the strength of association between two cancers and is calculated by dividing the observed incidence by the expected incidence of SPM (O/E ratio) in the general population (17). CI was calculated using the Poisson distribution assumption. AER is an absolute measure of the clinical burden of additional cancer occurrence in a given population. It measures the actual number of excess events normalized to the number of person years (PY) observed (AER=(O-E) PY).

About the SEER database. The SEER database collects comprehensive cancer data from hospitals and cancer treatment centers and maintains high quality data from defined geographical areas. It is a mature database with 98% case completeness. SEER 13 covers approximately 13.4% of the US population based on 2010 census. SEER 13 includes the following geographical areas: San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound),Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia.

Results

A total of 3,149 patients with MCL as first primary were included in the analysis. Among them, 2,124 (67.45%) were male. The median follow-up duration was 31 months (range=6 months to 16.25 years).

Among them, 261 (8.2%) patients developed 287 SPM with observed/expected (O/E) ratio of 1.32 (95% CI=1.17-1.48, $p<0.0001$) and AER of 54.32 per 10,000 population. Among solid tumors, there was a significant increase in the risk of melanoma of skin, other non-epithelial skin cancer and thyroid cancer. The patients had significantly higher risk of hematologic malignancies with an O/E ratio of 4.02 (N=76, CI=3.17-5.03, $p<0.0001$) and AER of 44.48 per 10,000 population. Risk of NHL (O/E ratio of 3.79 (N=35, CI=2.64-5.27, $p<0.0001$), AER 20.06), chronic lymphocytic leukemia (O/E ratio of 7.27 (N=20, CI=4.44-11.23, $p<0.0001$), AER 13.44) and acute myeloid leukemia (O/E ratio of 7.74 (N=15, CI=4.54-13.94, $p<0.0001$), AER 10.18) were significantly increased compared to the general population.

Second primary malignancy by latency. The median latency for SPM from the time of diagnosis of MCL was 47 months (range=6 months to 17.92 years). Anal carcinoma (O/E of 11.98 (N=2, CI=1.45-43.28, $p<0.01$), AER of 4.72) was increased within the first two years of latency. Similarly, risk of NHL (O/E of 2.59 (N=7, CI=1.04-5.33, $p<0.05$), AER of 11.04) and chronic lymphocytic leukemia (O/E of 6.24 (N=5, CI=2.03-14.57, $p<0.001$), AER of 10.8) was also increased within the first two years of latency. There was significantly increased risk of skin cancer (O/E of 2.43 (N=17, CI=1.41-3.89, $p<0.001$), AER 11.17), acute myeloid leukemia (O/E of 10.25 (N=14, CI=5.6-17.19, $p<0.0001$), AER 14.12), and NHL (O/E of 4.28 (N=28, CI=2.85-6.19, $p<0.0001$), AER of 23.98) after two years of latency.

Table I. *Patients' demographics*.

Demographics		N(%)/Median/Range	
Total number of patients	3,149		
Gender			
Male	2,124	(67.45)	
Female	1,025	(32.55)	
Race			
White	2,829	(89.84)	
Black	135	(4.29)	
Others	185	(5.87)	
Total number of SPM	287		
Total number of patients with SPM	261	8.29 percent of MCL patients	
Total number of patients with 1 SPM	237		
Gender			
Male	160	(67.51)	
Female	77	(32.49)	
Race			
White	203	(85.65)	
Black	18	(7.59)	
Others	16	(6.75)	
Total number of patients with two or more SPMs	24		
Gender			
Male	18	(75.00)	
Female	6	(25.00)	
Race			
White	23	(95.83)	
Black	1	(4.17)	
Others	0	(0.00)	
Age at the time of diagnosis of SPM	72	37.67 years	100.33 years
Latency to develop SPM	47	6 month	17.92 years
Follow-up time	31	6 month	16.25 years

SPM, Second primary malignancy.

Second primary malignancy by age. The median age for SPM was 71.5 years (range=37.67 years to 100.33 years). Younger patients (<60 years) had a higher risk of thyroid cancer (O/E of 9.29 (N=5, CI=3.02-21.67, $p<0.0001$), AER 11.86), NHL (O/E of 8.9 (N=9, CI=4.07-19.89, $p<0.001$), AER of 21.23), chronic lymphocytic leukemia (O/E of 9.2 (N=2, CI=1.11-33.24, $p<0.01$), AER of 4.74) and acute non-lymphocytic leukemia (O/E of 38.59 (N=6, CI=14.16-83.98, $p<0.001$), AER of 15.54). Older patients (60 years or more) had higher risk of skin cancer (O/E of 2.25 (N=19, CI=1.35-3.51, $p=0.001$), AER 11.63). The risk of NHL (O/E of 3.16 (N=26, CI=2.06-4.63, $p<0.001$), AER 19.58), chronic lymphocytic leukemia (O/E of 7.10 (N=18, CI=4.21-11.23, $p<0.0001$), AER 17.04) and acute non- lymphocytic leukemia (O/E of 5.05 (N=9, CI=2.31-9.59, $p<0.001$), AER of 7.95) were increased in older (>60 years) patients.

Table II. *Second primary malignancies in mantle cell lymphoma.*

	Total				
	Person at risk 3,149		Person Year at risk 12,836.86		
	N	O/E	Two-tail *p*-value	CI	Excess risk
All Sites	287	1.32	<0.0001	1.17-1.48	54.32
All Sites excluding Non-melonoma skin	281	1.30	<0.0001	1.15-1.46	50.44
All solid tumors	197	1.02	0.72	0.88-1.18	3.31
Brain	4	1.58	0.50	0.43-4.04	1.14
Head and neck cancer	8	1.09	0.63	0.47-2.15	0.53
Thyroid	6	3.00	<0.01	1.1-6.52	3.11
Lung and bronchus	37	1.17	0.28	0.83-1.62	4.29
Esophagus	2	0.74	0.98	0.09-2.67	–0.55
Stomach	5	1.24	0.44	0.4-2.88	0.74
Colon and rectum	20	0.87	0.61	0.53-1.34	–2.39
Anus, anal canal and anorectum	2	3.49	0.22	0.42-12.61	1.11
Hepato-biliary system	5	1.01	0.75	0.33-2.36	0.04
Pancreas	6	0.98	0.81	0.36-2.14	–0.07
Soft tissue, including heart	1	0.89	0.62	0.02-4.96	–0.1
Breast	9	0.53	0.053	0.24-1.01	–6.19
Female genital system	5	0.77	0.73	0.25-1.79	–1.17
Prostate	43	0.85	0.34	0.62-1.15	–5.69
Urinary system	27	1.3	0.15	0.85-1.89	4.81
Skin, excluding basal and squamous	22	2.24	<0.001	1.4-3.39	9.49
Hodgkin lymphoma	2	3.95	0.19	0.48-14.29	1.16
Non-Hodgkin lymphoma	35	3.79	<0.001	2.64-5.27	20.06
Myeloma	3	0.98	0.74	0.2-2.86	–0.05
Chronic lymphocytic leukemia	20	7.27	<0.001	4.44-11.23	13.44
Acute non-lymphocytic leukemia	15	7.74	<0.001	4.33-12.77	10.18

O/E, Observed/expected ratio; CI, confidence interval.

Discussion

The number of cancer survivors is increasing and is expected to be approximately 18 million by 2022 (18). Early diagnosis and improvement in effective treatment of cancer has led to an increase in the number of cancer survivors. SPM is an important and serious long-term complication in cancer survivors. Better understanding of SPM is important to guide post-treatment surveillance of cancer survivors. There is lack of evidence for evidence-based management of adult cancer survivors.

A recent meta-analysis on risk for SPMs in NHL survivors showed that risk of SPM is significantly higher in NHL (19). It showed that the relative risk of SPM was dependent on the therapy used for NHL. To the best of our knowledge, our study is the first to report the risk of SPM in MCL. Our study showed significantly higher risk of skin cancer, thyroid cancer, NHL, chronic lymphocytic leukemia and acute myeloid leukemia in adult patients with MCL. We found that the risk of specific SPM depends on the age of the patient and latency. Possible causes of increased risk of SPMs include exposure to chemotherapy, radiotherapy and stem cell transplant. There is a higher risk of post-transplant malignancies, which continues to increase even 20 years after transplant (20). In a large multi-institutional study, allogeneic hematopoietic stem cell transplant recipients developed new solid tumors at significantly higher rates compared to that expected (O/E ratio=2.1, 95% CI=1.8-2.5, with p-value for trend<0.001) in the general population (21).

Strengths of our study include high quality data with large sample size and long-term follow-up. There are several limitations. The SEER program does have data on chemotherapy used, patient's co-morbidities, family history and other risk factors, such as smoking, alcohol use and exposure to other carcinogens. Similarly, a small number of recurrences in certain anatomic locations may be misclassified as SPM. There is a potential for under-estimation of SPM risk in case of migration of patient out of SEER geographic registry.

In summary, our study showed increased risk of SPM in patient with MCL. The risk of specific cancer depends on the age of patient at diagnosis and latency period. These findings suggest that evaluation of SPM should be an important part of follow-up examination of MCL survivors.

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