Second Primary Malignancies in Adult Acute Myeloid Leukemia - A US Population-based Study

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Abstract. *Background: Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. Long-term survivors from AML may be at higher risk of second primary malignancies. Patients and Methods: We selected adult patients with AML aged ≥18 years from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER 13) database. We used the multiple primary standardized incidence ratio session of SEER*stat software to calculate the risk of second primary malignancies in patients with AML. Results: Among 5,091 patients, 148 patients developed a total of 160 second primary malignancies, with an observed/expected (O/E) ratio of 1.17, (95% confidence interval=0.99-1.36), and an excess risk of 15.47 per 10,000 population. The risk of all-site cancer, cancer of gastrointestinal system, and oral and pharyngeal cancer in different age groups was found to be significantly higher among patients with AML compared to that of general US population. Conclusion: Adult patients with AML have a significantly higher risk of second primary malignancies compared to the general population.*

Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults. The National Cancer Institute (NCI) estimates approximately 13,780 new cases of AML in 2012 (1). AML is a curable disease. Standard treatment for patients younger than 60 years includes induction chemotherapy with '7+3' chemoregimen followed by consolidation therapy with 3-4 high-dose cytarabine or matched sibling or unrelated donor hematopoietic stem cell transplantation. Consolidation therapy with high-dose cytarabine is based on the findings of the Cancer and Leukemia Group B trial that compared 100 mg/m^2, 400 mg/m^2 and 3 g/m^2 doses of cytarabine in patients who had achieved complete remission with three days of daunorubicin and seven days of cytarabine induction therapy (2). Forty-four percent of patients who received high-dose cytarabine (3 g/m^2) had 4-year disease-free survival. A subsequent analysis showed 5-year relapse-free survival of 78% in core binding factor AML, 40% for those with normal karyotype and 21% for those in other cytogenetic categories. Similarly, 5-year survival with allogeneic hematoloeptic stem cell transplant is higher than 40% among younger patients with AML with unfavorable cytogenetics (3). Survival of patients with AML has improved, and is attributed to improvement in supportive therapy (4, 5). Several studies have shown that there is an increased risk of second primary malignancies (SPM) after treatment of primary cancer (6-13). As the number of survivors after AML is increasing, it is important to evaluate the risk of SPM in this population. We conducted this study to analyze the risk of SPM in patients with AML older than 18 years of age from Surveillance, Epidemiology and End Results (SEER) database.

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Patients and Methods

We evaluated the risk of SPM in patients diagnosed with primary AML reported in the SEER 13 Regs Research Data, November 2012 Sub (1992-2010) database (14) released in April 2013. We selected adult patients aged 18 years or more at the time of diagnosis, and who were diagnosed with AML from January 1992 to December 2010. Patients were followed-up from diagnosis of AML to the date of last known vital status, death, or the last point of data collection. We excluded cases diagnosed at autopsy and those who did not have follow-up. Patients with second malignancy diagnosed within six months of diagnosis of AML were also excluded. Using the Warren and Gates criteria (15) as modified by the NCI (16), SPM was defined as a metachronous malignancy developing six months or more after an index AML.

We used multiple primary standardized incidence ratio (MP-SIR) session to find the incidence of SPM in patients with AML during the given time period. We used the SEER*stat software, Version 8.0.4 - April 15, 2013 to calculate the standardized incidence ratio (SIR), excess risk, and confidence interval (CI) for SPM in patients previously diagnosed with AML. Patients with newly-diagnosed AML were followed over the given time to calculate absolute or observed SPM. The expected SPM was calculated for a reference SEER cohort of identical age, sex and time period.

Table I. *Demographics of patients*.

	No. (%)/Median (range)
Total no. of patients with AML 5,091	
Gender	
Male	2,769 (54)
Female	2,322 (46)
Race:	
White	4,066 (79.8)
Black	436 (8.6)
Other	589 (11.6)
Total number of SPM	160
Total no. of patients with SPM	148 (2.9% of the study population)
Total number of patients with 1 SPM	137
Male	80 (58)
Female	57 (42)
Race	
White	117 (85)
Black	8 (6)
Other	12 (9)
Total number patients with ≥2 SPMs	(11)
Male	8 (73)
Female	3 (27)
Race	
White	9 (82)
Black	1 (9)
Other	1 (9
Age at the time of diagnosis of SPM, years	68.46 years (35.33-93.41 years)
Latency to develop SPM	3.25 years (6 months-16.9 years)
Follow-up time	4.21 years (6 months-18.38 years)

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

About the SEER database. The SEER database is the largest cancer registry of the NCI. 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 (18). SEER 13 covers approximately 13.8% of the US population. The geographical areas covered in this registry include: San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, and Rural Georgia.

Results

A total of 11,216 adult patients diagnosed with primary AML during 1992-2010 were reported in the SEER 13 registry. With exclusion of 281 patients with index record dates after the cut-off date and 5,844 patients with a date of last contact within

Table II. *Number of second primary malignancies by race*.

No. of SPM	White N (%)	Black N (%)	Other N (%)
0	3,940 (96.9)	427 (97.94)	576 (97.79)
1	117 (2.88)	8 (1.83)	12 (2.04)
2	8 (0.2)	1 (0.23)	1 (0.17)
3+	1 (0.02)	0 (0)	0 (0)
Total	4,066 (100)	436 (100)	589 (100)

N: Number of patients who developed SPM.

Table III. *Number of second primary malignancies by age*.

No of SPM	Age					
	≥18 years		≥18-60 years		≥61 years	
	N	%	N	%	N	%
0	4,943	97.09	2,624	97.98	2,319	96.1
1	137	2.69	48	1.79	89	3.69
2	10	0.2	6	0.22	4	0.17
3+	1	0.02	0	0	1	0.04
Total	5,091	100	2,678	100	2,413	100

Table IV. *Second primary malignancies with latency and age.*

	Latency											Age										
	6-23 months persons at risk: 5,091; person years: 4,505.51					24+ months persons at risk: 1,984; person years: 10,145.39						18-60 years persons at risk: 2,678; person years: 11,003.69						61+ years persons at risk: 2,413; person years: 3,647.20					
SPM	N	O/E	*p*-Value	CI	ER	N	O/E	*p*-Value	CI		ER	N	O/E	*p*-Value	CI		ER	N	O/E	*p*-Value	CI		ER
All sites	58	1.18	0.241	0.89-1.52	19.46	102	1.16	0.158	0.94	1.41	13.7	60	1.03	0.857	0.79	1.33	1.56	100	1.27	0.026	1.03	1.54	57.45
All sites excluding non-melonoma skin	57	1.16	0.288	0.88-1.51	17.66	101	1.15	0.178	0.94	1.4	13.05	60	1.03	0.837	0.79	1.33	1.74	98	1.24	0.040	1.01	1.52	52.86
All solid tumors	51	1.16	0.327	0.86-1.52	15.52	88	1.12	0.333	0.89	1.37	8.96	52	0.99	1.008	0.74	1.3	–0.53	87	1.24	0.068	0.99	1.53	45.71
Oral cavity and pharynx	0	0	0.646	0-3.28	–2.5	9	4.37	0.0006	2	8.3	6.84	7	4.34	0.002	1.74	8.94	4.9	2	1.27	0.930	0.15	4.59	1.17
Digestive system	16	1.69	0.064	0.97-2.75	14.54	17	1.05	0.892	0.61	1.69	0.86	6	0.63	0.330	0.23	1.37	–3.18	27	1.68	0.016	1.11	2.44	29.96
Small intestine	1	5.34	0.346	0.14-29.73	1.8	1	2.77	0.605	0.07	15.43	0.63	1	4.05	0.442	0.1	22.55	0.68	1	3.32	0.518	0.08	18.49	1.92
Respiratory system	13	1.72	0.089	0.92-2.95	12.11	15	1.2	0.540	0.67	1.99	2.51	10	1.48	0.288	0.71	2.73	2.96	18	1.36	0.247	0.8	2.15	13.01
Female breast	1	0.19	0.058	0-1.03	–9.76	14	1.13	0.729	0.62	1.89	1.56	11	1.09	0.859	0.54	1.95	0.82	4	0.52	0.235	0.14	1.33	–10.18
Female genital system	1	0.47	0.754	0.01-2.64	–2.47	2	0.42	0.283	0.05	1.5	–2.77	2	0.51	0.500	0.06	1.85	–1.74	1	0.33	0.398	0.01	1.85	–5.49
Ovary	1	1.73	0.880	0.04-9.66	0.94	0	0	0.562	0	2.9	–1.25	1	1.04	1.234	0.03	5.8	0.04	0	0	0.821	0	4.16	–2.43
Prostate	10	0.94	1.004	0.45-1.73	–1.45	15	0.92	0.867	0.51	1.51	–1.32	5	0.5	0.128	0.16	1.16	–4.62	20	1.18	0.512	0.72	1.83	8.46
Urinary system	8	2	0.103	0.86-3.93	8.86	7	1.03	1.04	0.41	2.12	0.2	6	1.54	0.399	0.56	3.35	1.91	9	1.3	0.518	0.6	2.47	5.74
Kidney	6	4.92	0.003	1.81-10.71	10.61	1	0.41	0.612	0.01	2.31	–1.39	3	1.71	0.517	0.35	4.99	1.13	4	2.14	0.240	0.58	5.47	5.83
Endocrine	2	3.17	0.264	0.38-11.45	3.04	0	0	0.365	0	2.17	–1.68	2	1.16	1.038	0.14	4.2	0.26	0	0	1.075	0	5.99	–1.69
Thyroid	2	3.43	0.231	0.42-12.4	3.15	0	0	0.404	0	2.3	–1.58	2	1.23	0.969	0.15	4.43	0.34	0	0	1.154	0	6.66	–1.52
All lymphatic and hematopoietic diseases	6	1.5	0.430	0.55-3.27	4.44	12	1.65	0.132	0.85	2.89	4.67	8	1.71	0.205	0.74	3.38	3.03	10	1.52	0.261	0.73	2.79	9.36
Other	0	0	0.069	0-1.1	–7.46	9	1.43	0.366	0.66	2.72	2.68	3	0.66	0.681	0.14	1.94	–1.38	6	1.17	0.814	0.43	2.55	2.39

N: Observed number of SPM; ER: excess risk per 10,000; CI: 95% confidence intervals.

the latency exclusion period, 5,091 patients were included for analysis. Out of these, 2,769 (54%) were male; the median follow-up time was 4.21 years (range=6 months to 18.38 years). Patients' characteristics are summarized in Table I. A total of 148 (2.9%) patients developed SPM six months after diagnosis of primary AML. Out of them, 58(39%) were alive at the end of study. One hundred and thirty seven patients with AML developed only one SPM and 10 patients developed two SPMs. SPM was more common in males compared to females (3.2% vs 2.6%). The number of SPMs by race and age is shown in Tables II and III.

The total number of all-site SPM among all adult patients with AML reported during same time period was 160, with an O/E ratio of 1.17 (95% CI=0.99-1.36), and an excess risk of 15.47 per 10,000 population. The risk of oral cavity and pharyngeal cancer was significantly increased in patients with AML with O/E: 2.83 (CI=1.29-5.36; p=0.01), and an excess risk of 3.97 per 10,000 populations. Increase in oral cavity and pharyngeal was particularly seen in younger patients with AML. For older patients, there was a significant increase in all-site cancer, as well as cancer of the digestive system (Table IV).

SPM by latency. The median time-to-first SPM from the time of diagnosis of AML was 37.5 months (range=6-203 months). The trend for development of SPM was: 0.5% at completion of six months, 25% by 14 months, 50% by 37.5 months and 75% by 87.5 months. The median time-to-development of a second SPM after diagnosis of the first SPM was 23 months (range=0-83 months).

Kidney cancer was significantly increased during 6-24 months among adult patients with AML. This increment was seen particularly among older patients with AML (O/E=4.49, CI=1.22-11.51, p=0.02, Excess risk 17.68 per 10,000 population) as compared to the general population. After 24 months from diagnosis of AML, oral cavity and pharyngeal cancer was significantly increased among all adult patients with AML and particularly in younger patients with AML. All-site cancer was significantly increased in older patients with AML after 24 months of diagnosis of AML as compared to the general population (Table IV).

The median age at the time of diagnosis of all SPM was 68.46 years (range=35.33-93.41 years), and at diagnosis of first SPM 68.2 years (range=35.33-93.41 years); 10% developed SPM by 48.4 years of age, 25% by 59.12 years of age, 50% by 68.2 years of age, and 75% by 76.3 years of age. The median age of patients with AML at diagnosis of second SPM was 70.25 years (range=38.1-90 years).

Discussion

Due to improvement in treatment, the number of survivors after AML is increasing (19). There are limited data on SPMs in patients with AML. Our study showed a 17% relative increase in SPM in patients with AML (SIR=1.17, 95% CI=0.99-1.36) compared to the general population. In view of the significant increase in oral cavity and pharyngeal cancer in young adults, and gastrointestinal cancer in older adults, follow-up examination of AML survivors should focus on early diagnosis of these cancer types in these age groups. Previous study by Pagano *et al.* failed to show significantly increased risk of SPM in the overall AML population (20). When analyzed by age, patients younger than 60 years had a three-fold higher rate of SPM (SIR=3.63, 95% CI=1.56-7.15). The median latency for SPM was 50.7 months (range=2.8-87.8 months), which was similar to our study. Lung and breast followed by bowel cancer were the most common type of SPM noted in this study.

Another study in childhood AML showed a 10-fold greater risk of SPM than for the general population (21). Since the biology of AML in adult patients is different, SPM in the pediatric population may not accurately reflect SPM in the adult population.

There may be several reasons for a significantly higher risk of SPM in patients with AML. Chemotherapy is well-known as a risk factor for cancer. Similarly, many young patients with AML receive hematopoetic stem cell transplantation as consolidation therapy. There is a higher risk of post-transplant malignancies, and this continues to increase even 20 years after transplant (22). In a large multi-institutional study, allogeneic hematopoetic 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 (23).

In summary, this study showed that adult patients with AML are at a significantly higher risk of SPM. The risk of specific SPM depends on the age of the patient and the latency period. As survival of patients with AML is improving, it is important to be aware of long-term complications, including SPM, in this population. This will help us in effectively devising strategies to identify and treat these complications at an earlier stage.

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