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Association of Chemotherapy for Solid Tumors With Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era

Lindsay M. Morton, PhD; Graça M. Dores, MD, MPH; Sara J. Schonfeld, PhD, MPH; Martha S. Linet, MD, MPH; Byron S. Sigel, BA; Clara J. K. Lam, PhD; Margaret A. Tucker, MD; Rochelle E. Curtis, MA

IMPORTANCE Therapy-related myelodysplastic syndrome or acute myeloid leukemia (tMDS/AML) is a rare, usually fatal complication of chemotherapy, including certain alkylating agents, topoisomerase II inhibitors, and platinum compounds. With the introduction of new chemotherapeutic agents, expanded indications for established agents, and increased neoadjuvant and adjuvant chemotherapy, tMDS/AML risks in the modern age are poorly understood.

OBJECTIVES To quantify tMDS/AML risk after chemotherapy for solid cancer among United States adults since 2000 and correlate tMDS/AML risk patterns with chemotherapy treatment practices.

DESIGN, SETTING, AND PARTICIPANTS A population-based cohort study was conducted using cancer registries from the Surveillance, Epidemiology, and End Results (SEER) Program and Medicare claims. Risk analyses included 1619 tMDS/AML cases among 700 612 adults (age, 20-84 years) who were diagnosed with first primary solid cancer during 2000 to 2013 (followed up through 2014), received initial chemotherapy, and survived 1 year or longer, as reported to SEER. Descriptive analyses were conducted of SEER records linked with Medicare claims for chemotherapy in 165 820 older adults (age, 66-84 years) receiving initial chemotherapy for a first primary solid cancer in 2000-2013. Data analysis was conducted from October 2017 to April 2018.

EXPOSURES Receipt of initial chemotherapy for solid cancer.

MAIN OUTCOMES AND MEASURES Second primary tMDS/AML.

RESULTS Based on 1619 tMDS/AML cases in the SEER database (mean [SD] age, 64.3 [12.2] years; 1148 [70.9%] female), tMDS/AML risks were statistically significantly elevated after chemotherapy for 22 of 23 solid cancers (all except colon). Relative risks ranged from 1.5 to greater than 10 and excess absolute risks from 1.4 to greater than 15 cases per 10 000 person-years compared with the general population. Overall survival following tMDS/AML diagnosis was poor (1270 of 1619 patients [78.4%] died; median overall survival, 7 months). For patients treated with chemotherapy at the present time, approximately three-quarters of tMDS/AML cases expected to occur within the next 5 years will be attributable to chemotherapy. In the SEER-Medicare database, use of known leukemogenic agents, particularly platinum compounds, in initial chemotherapy increased substantially since 2000, most notably for gastrointestinal tract cancers (esophagus, stomach, colon, and rectum; 10% in 2000-2001 to 81% during 2012-2013).

CONCLUSIONS AND RELEVANCE Large-scale, United States population-based data demonstrate excess tMDS/AML risks following chemotherapy for nearly all solid tumor types, consistent with expanded use of known leukemogenic agents in the 21st century. Continued efforts to reduce treatment-related adverse events, particularly for solid cancer patients with favorable prognosis, are needed.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Lindsay M. Morton, PhD, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 9609 Medical Center Dr, Room 7E-454, MSC 9778, Bethesda, MD 20892 (mortonli@mail.nih.gov).

The 21st century has seen substantial changes in the agents and clinical approaches to cancer chemotherapy, with corresponding improvements in prognosis for many cancers.[1] However, the longer-term balance of benefits and risks of new treatment approaches often are not well understood because clinical trials for many cancers lack sufficient sample size and long-term patient follow-up. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), a clonal hematopoietic stem cell neoplasm that can transform to AML, are rare, usually fatal complications of cancer therapy. Certain alkylating agents (eg, melphalan), platinum compounds (eg, cisplatin), and topoisomerase II inhibitors (eg, etoposide) have been reported to confer more than 5-fold increased risks for therapy-related MDS or AML (tMDS/AML), whereas other alkylating agents have lower risks (eg, cyclophosphamide), and other classes of agents, such as fluoropyrimidines (eg, fluorouracil), have no apparent association.[2-4] Radiotherapy has been associated with tMDS/AML, although the exact magnitude of risk is unclear.[5]

We undertook an investigation to quantify tMDS/AML risks after chemotherapy for solid tumors in the modern treatment era (2000-2014) using United States population-based cancer registry data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Advantages of these registry data include large numbers of unselected patients treated with chemotherapy, systematic long-term patient follow-up, and ability to compare tMDS/AML incidence among patients treated with chemotherapy with the general population to estimate relative and absolute risks. Then, we used a linkage between SEER and Medicare claims to provide descriptive information on specific chemotherapeutic agents used in the initial treatment of each primary cancer during the study period (January 1, 2000, to December 31, 2014). Data analysis was conducted from October 2017 to April 2018.

Key Points

Question What is the association of therapy-related myelodysplastic syndrome or acute myeloid leukemia (tMDS/AML) with chemotherapy for solid cancer in the modern treatment era?

Findings In this population-based study of 700 612 adults in a US cancer data registry, based on 1619 tMDS/AML cases, the risk of tMDS/AML was significantly increased 1.5-fold to more than 10-fold after chemotherapy for 22 of 23 solid cancer types investigated (all except colon cancer).

Meaning Although tMDS/AML is rare, gains in solid cancer survival from modern treatment approaches should be balanced against tMDS/AML risks and other chemotherapy-related adverse effects; continued efforts to develop effective agents and cancer treatment approaches with fewer late sequelae are needed.

Methods

SEER Registry Data: tMDS/AML Risk

Study Population

We quantified tMDS/AML risk among adults (age, 20-84 years) whose first primary solid cancer was diagnosed during 2000-2013 in 1 of 17 SEER registry areas and who survived 1 year or more without developing a second cancer (eMethods in the Supplement).[1] We further restricted the study population to patients who received initial chemotherapy as reported to the cancer registries; information on specific agents and chemotherapy use after initial treatment is not available in the SEER database. Analyses included first primary solid cancers in which more than 10% of patients received initial chemotherapy (eTable 1 in the Supplement). This research was excluded from ethics committee review by the National Institutes of Health Office of Human Subjects Research because it relied on deidentified existing data.

Patients were followed up beginning 1 year after the first primary cancer diagnosis (to reduce second cancer overascertainment during the first year owing to heightened surveillance) until the second cancer diagnosis, death, age 85 years, loss to follow-up, or end of the study (December 31, 2014), whichever came first.[6] Second primary tMDS/AML was identified using *International Classification of Diseases for Oncology, Third Edition* morphology codes (eTable 2 in the Supplement),[7,8] considering both tMDS, which may progress to AML, and tAML. SEER registry data do not specify whether tAML diagnoses were associated with preceding tMDS. The term *tMDS/AML* describes all second primary MDS/AML occurring among patients previously treated with initial chemotherapy for cancer, in accordance with the World Health Organization.[7,8] Comprehensive data on cytogenetics were not available.

SEER-Medicare Data: Patterns of Chemotherapy Use

Because registry data do not include treatment details, we used an alternative database to provide descriptive information on population-based patterns of chemotherapeutic drug use from 2000 to 2013. Chemotherapy agents were recorded for each patient from the SEER-Medicare database, which links Medicare claims—the federally supported health insurance program for older US adults (aged ≥65 years)—with SEER population-based cancer registry data.[9]

To ensure completeness of chemotherapy information, we restricted the study to individuals with continuous Medicare coverage 2 months before through 12 months following their first primary cancer diagnosis during 2000-2013 at ages 66 to 84 years. In addition, patients were required to survive 1 year or more without developing a second primary cancer, comparable to the SEER analysis.

Statistical Analysis

Relative risk of tMDS/AML compared with the general population was estimated by the standardized incidence ratio (SIR) (observed/expected) with exact, Poisson-based 95% CIs determined using SEER*Stat software, version 8.3.4 (National Cancer Institute).[10,11] Expected numbers of cases were derived from MDS/AML incidence rates in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, or other), sex, and calendar year (3 groups), multiplied by the appropriate person-years at risk. For each first primary cancer, SIRs were estimated overall and by time since diagnosis, age at diagnosis, receipt of initial chemoradiotherapy vs chemotherapy

Table 1. Risk for tMDS/AML After Initial Chemotherapy, Overall and by Interval From First Primary Cancer Diagnosis[a]

First Primary Cancer	Patients, No.	Overall			By Interval From First Primary Cancer				
					1.0-4.9 y		≥5 y		
		Observed, No.	SIR (95% CI)[b]	EAR[c]	Observed, No.	SIR (95% CI)[b]	Observed, No.	SIR (95% CI)[b]	*P* Value[d]
Oral cavity/pharynx	32 523	61	2.4 (1.8-3.1)	3.0	39	2.5 (1.8-3.4)	22	2.3 (1.4-3.5)	.63
Esophagus	12 113	34	3.9 (2.7-5.5)	9.9	31	5.1 (3.5-7.2)	3	1.2 (0.2-3.5)	.003
Stomach	16 124	29	2.7 (1.8-3.8)	4.7	25	3.4 (2.2-5.0)	4	1.1 (0.3-2.9)	.01
Colon	69 787	83	1.1 (0.9-1.3)	0.2	52	1.2 (0.9-1.5)	31	1.0 (0.7-1.4)	.26
Rectum/rectosigmoid junction	50 081	84	1.5 (1.2-1.9)	1.4	45	1.4 (1.0-1.9)	39	1.6 (1.2-2.2)	.76
Anus/anal canal/anorectum	9373	30	3.6 (2.4-5.1)	5.4	19	4.0 (2.4-6.2)	11	3.0 (1.5-5.4)	.26
Liver	12 021	15	2.6 (1.4-4.2)	3.7	12	2.6 (1.4-4.6)	3	2.4 (0.5-6.9)	.87
Pancreas	17 800	18	2.9 (1.7-4.6)	5.3	13	2.6 (1.4-4.4)	5	4.7 (1.5-11.0)	.23
Peritoneum	3317	16	7.5 (4.3-12.2)	15.8	10	6.2 (3.0-11.4)	6	11.7 (4.3-25.5)	.14
Larynx	7628	22	3.4 (2.2-5.2)	6.3	16	3.9 (2.2-6.3)	6	2.7 (1.0-5.8)	.32
Small cell lung/bronchus	20 571	69	8.1 (6.3-10.3)	19.9	51	8.0 (6.0-10.5)	18	8.4 (5.0-13.3)	.69
Non-small cell lung/bronchus	84 100	171	3.5 (3.0-4.1)	7.7	126	3.4 (2.8-4.0)	45	4.0 (2.9-5.3)	.96
Bones/joints	1497	14	39.0 (21.4-65.5)	23.6	11	52.9 (26.4-94.7)	3	19.9 (4.1-58.1)	.71
Soft tissue (including heart)	4313	21	10.4 (6.4-15.9)	12.6	17	14.4 (8.4-23.0)	4	4.8 (1.3-12.2)	.03
Female breast	249 526	669	3.8 (3.5-4.1)	3.6	461	5.3 (4.8-5.8)	208	2.3 (2.0-2.6)	<.001
Cervix	15 758	27	4.0 (2.6-5.8)	3.1	19	5.1 (3.1-8.0)	8	2.6 (1.1-5.2)	.05
Corpus uteri	15 496	43	4.6 (3.3-6.2)	7.0	39	6.2 (4.4-8.4)	4	1.3 (0.4-3.4)	<.001
Ovary	32 662	113	5.8 (4.8-6.9)	8.2	61	4.7 (3.6-6.1)	52	7.8 (5.8-10.2)	.10
Vagina/vulva	1914	5	4.0 (1.3-9.3)	5.6	4	5.2 (1.4-13.2)	<3	[d]	[d]
Fallopian tube	1699	11	8.7 (4.3-15.5)	16.0	7	8.6 (3.5-17.7)	4	8.8 (2.4-22.5)	.93
Testis	8052	21	12.3 (7.6-18.8)	4.4	17	21.0 (12.2-33.6)	4	4.5 (1.2-11.4)	.001
Bladder	18 789	40	1.6 (1.2-2.2)	2.8	30	1.7 (1.2-2.5)	10	1.4 (0.7-2.6)	.39
Brain/CNS	15 468	23	7.2 (4.6-10.8)	6.0	14	5.6 (3.1-9.4)	9	12.9 (5.9-24.5)	.41

Abbreviations: CNS, central nervous system; EAR, excess absolute risk; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; tMDS/AML, therapy-related myelodysplastic syndrome or acute myeloid leukemia.

[a] Among 700 612 adults (aged 20-84 years) who received initial chemotherapy for first primary solid cancer and survived 1 or more years after first primary cancer diagnosis, 17 SEER registries, 2000-2013 (followed up through 2014). eTable 1 in the Supplement provides patient characteristics.

[b] SIR, observed/expected. Expected numbers of cases were derived from incidence rates for MDS/AML in the total population of the same 17 SEER registries, stratified by age (5-year groups), race (white/unknown, black, or other), sex, and calendar year (3 groups), multiplied by the appropriate person-years at risk. Exact numbers of observed cases less than 3 and accompanying SIRs were not shown to protect patient confidentiality.

[c] EAR, (observed − expected) × 10 000 per person-years.

[d] Multivariable Poisson regression models adjusted for sex and age at first primary cancer diagnosis (<50, 50-64, or 66-84 years) through stratification were used to conduct a 2-sided test for homogeneity in SIRs by interval from first primary cancer using a likelihood ratio statistic in which the log of the expected number of cases was included as an offset to indirectly adjust for attained age and calendar year.[12,13] Models were not constructed when 1 group had fewer than 3 cases owing to insufficient sample size.

alone, and stage. Multivariable Poisson regression models tested for statistically significant (2-sided $P < .05$) differences in SIRs by patient subgroup using a likelihood ratio statistic in which the log of the expected number of cases was included as an offset to indirectly adjust for attained age and calendar year (Epicure, version 2.0; Risk Sciences International) (eMethods in the Supplement; **Table 1**).[12,13] We also estimated tMDS/AML excess absolute risk (EAR) ([observed - expected] × 10 000/person-years) (SEER*Stat software, version 8.3.4), cumulative incidence of tMDS/AML considering death and diagnosis of other second cancers as competing risks (Stata, version 13.1; StataCorp),[14] and median overall survival following tMDS/AML diagnosis (SAS, version 9.3; SAS Institute Inc).

Analyses of chemotherapeutic drug use included first primary solid cancers in which more than 10% of patients received initial chemotherapy (eTable 3 in the Supplement). We excluded testis and bone cancers owing to small sample size in the SEER-Medicare database. We ascertained Medicare claims for parenterally administered initial chemotherapy (<12 months following cancer diagnosis), focusing on known leukemogenic agents (alkylating agents, platinum compounds, and topoisomerase II inhibitors) (eTable 4 in the Supplement provides claims codes). The SEER-Medicare database incompletely captures orally administered agents (eg, cyclophosphamide, temozolomide) and does not capture doses or duration of use. We calculated the percentage of patients receiving chemotherapy (any, by class of agents, and by specific agent) by calendar year of cancer diagnosis, overall and by stage (SAS, version 9.3). The SEER-Medicare data were not used to directly estimate tMDS/AML risk.

Results

SEER Registry Data: tMDS/AML Risk

We investigated the risk for tMDS/AML among 700 612 adults (age, 20-84 years) initially treated with chemotherapy for 1 of 23 first primary solid cancers during 2000-2013 (followed up

Table 2. Risk for tMDS/AML by Receipt of Initial Radiotherapy[a]

First Primary Cancer[b]	Patients, No.	By Receipt of Initial Radiotherapy[b]								P Value[d]
		Any Chemoradiotherapy				Chemotherapy Without Known Radiotherapy				
		Patients, No. (%)	Latency, y[c]	Observed, No.	SIR (95% CI)	Patients, No. (%)	Latency, y[c]	Observed, No.	SIR (95% CI)	
Esophagus	12 113	10 130 (83.6)	3.0	28	3.6 (2.4-5.3)	1983 (16.4)	2.8	6	6.5 (2.4-14.2)	.68
Stomach	16 124	8763 (54.3)	2.8	23	3.3 (2.1-4.9)	7361 (45.7)	3.0	6	1.5 (0.6-3.4)	.03
Rectum/ rectosigmoid junction	50 081	38 316 (76.5)	5.1	65	1.4 (1.1-1.8)	11 765 (23.5)	5.2	19	1.9 (1.1-2.9)	.22
Pancreas	17 800	7835 (44.0)	4.2	9	2.8 (1.3-5.4)	9965 (56.0)	3.7	9	3.0 (1.4-5.8)	.81
Small cell lung/bronchus	20 571	14 286 (69.4)	3.5	58	9.0 (6.8-11.6)	6285 (30.6)	2.8	11	5.3 (2.7-9.5)	.07
Non-small cell lung/bronchus	84 100	49 112 (58.4)	3.6	117	4.4 (3.6-5.2)	34 988 (41.6)	4.0	54	2.5 (1.9-3.2)	.001
Bones/joints	1497	422 (28.2)	3.0	4	42.1 (11.5-107.7)	1075 (71.8)	4.0	10	38.0 (18.2-69.8)	.45
Soft tissue (including heart)	4313	2460 (57.0)	3.3	13	10.3 (5.5-17.6)	1853 (43.0)	3.3	8	10.6 (4.6-20.9)	.85
Female breast	249 526	144 312 (57.8)	4.0	448	4.3 (3.9-4.7)	105 214 (42.2)	4.3	221	3.1 (2.7-3.5)	<.001
Corpus uteri	15 496	7992 (51.6)	2.9	22	4.2 (2.6-6.4)	7504 (48.4)	4.0	21	5.1 (3.2-7.8)	.75
Bladder	18 789	2591 (13.8)	3.7	9	3.0 (1.4-5.6)	16 198 (86.2)	3.9	31	1.5 (1.0-2.1)	.06

Abbreviations: CNS, central nervous system; NS, not shown; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; tMDS/AML, therapy-related myelodysplastic syndrome or acute myeloid leukemia.

[a] Among 700 612 adults (aged 20-84 years) who received initial chemotherapy for first primary solid cancer and survived 1 or more years after first primary cancer diagnosis, 17 SEER registries, 2000-2013 (followed up through 2014). eTable 1 in the Supplement provides patient characteristics.

[b] SIRs by receipt of initial radiotherapy are not shown for those first primary cancers (oral cavity/pharynx, colon, anus/anal canal/anorectum, liver, peritoneum, larynx, cervix, ovary, vagina/vulva, fallopian tube, testis, and brain/CNS) in which less than 10% or more than 90% of patients received radiotherapy due to insufficient sample size for stratified analyses.

[c] Mean time from first primary cancer diagnosis until tMDS/AML.

[d] Multivariable Poisson regression models adjusted for sex, age at first primary cancer diagnosis (<50, 50-64, and 66-84 years), and time since first primary cancer diagnosis (<5 and ≥5 years) through stratification were used to conduct a 2-sided test for homogeneity in SIRs by receipt of initial radiotherapy using a likelihood ratio statistic, in which the log of the expected number of cases was included as an offset to indirectly adjust for attained age and calendar year.[12,13]

through 2014) (eTable 1 in the Supplement). The mean age at diagnosis was 50 years or older except for patients with bone, soft tissue, and testis cancers. Five-year relative survival generally was consistent for cases diagnosed during 2000-2006 vs 2007-2013.

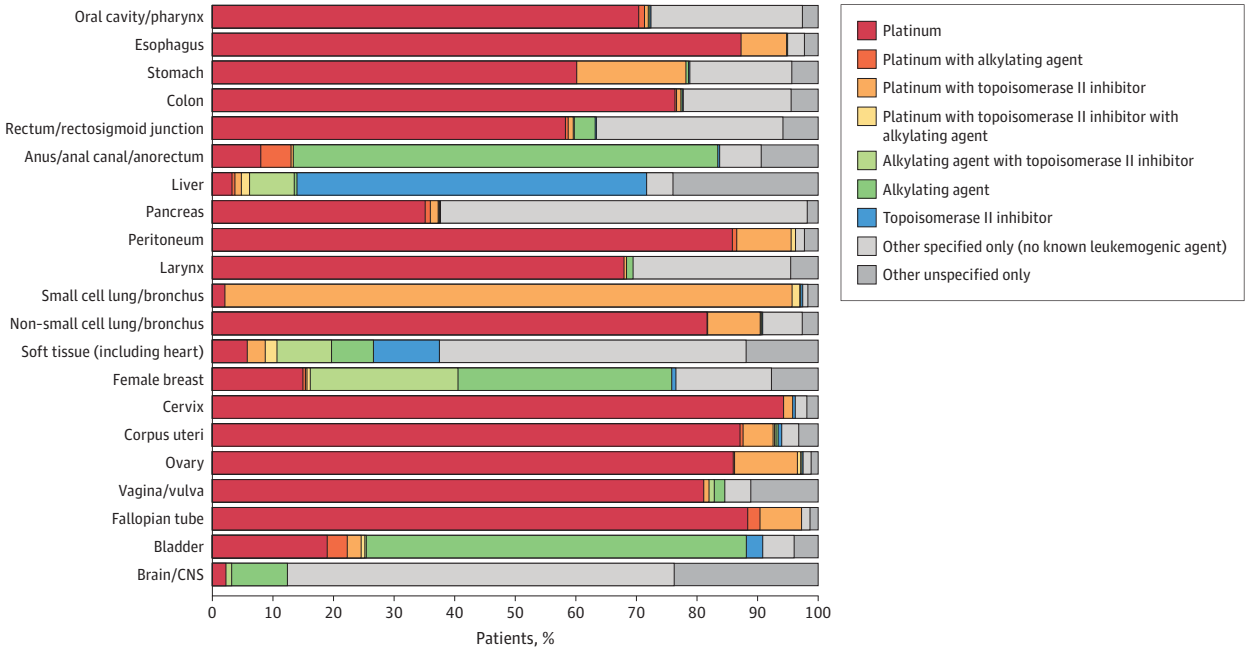
Based on a total of 1619 cases (64.3 [12.2] years; 1148 [70.9%] female), tMDS/AML occurred statistically significantly more often than expected after initial chemotherapy for each first primary solid cancer except colon cancer (Table 1). Relative risks were the highest (>10) after chemotherapy for bone (SIR, 39.0; 95% CI, 21.4-65.5), soft tissue (SIR, 10.4; 95% CI, 6.4-15.9), and testis (SIR, 12.3; 95% CI, 7.6-18.8) cancers, which were typically diagnosed in younger patients. Otherwise, SIRs were 5- to 9-fold significantly elevated following chemotherapy for peritoneum, small cell lung, ovary, fallopian tube, and brain or central nervous system cancers and 1.5-fold to 4-fold significantly elevated following chemotherapy for the remaining cancers.

The tMDS/AML risks were not significantly elevated after chemotherapy for colon cancer overall (SIR, 1.1; 95% CI, 0.9-1.3) or in the more recent time period (2007-2014; n = 28 cases; SIR, 1.2; 95% CI, 0.8-1.8) (eTable 5 in the Supplement). In analyses of tMDS (mean time to development, 4.6 years) and tAML (mean time to development, 3.8 years) separately, SIRs were broadly consistent, although tAML risks appeared to be somewhat higher than tMDS risks following chemotherapy for some cancers, such as small cell lung and female breast (eTable 6 in the Supplement).

Using multivariable Poisson models, we found statistically significantly higher tMDS/AML risks fewer than 5 vs 5 years or more after diagnosis of esophagus, stomach, soft tissue, female breast, uterine corpus, and testis cancers (Table 1). However, SIRs remained statistically significantly elevated 5 years or more after diagnosis for 15 of the 23 first primary cancers. SIRs were statistically significantly higher among patients who received initial chemoradiotherapy vs chemotherapy alone for stomach, non-small cell lung, and female breast cancers but not for other first primary types evaluated (**Table 2**). In additional analyses by patient subgroup, tMDS/AML SIRs were consistently highest for younger ages at first primary cancer diagnosis but generally remained significantly elevated for patients whose cancer was diagnosed at older ages (≥65 years) (eTable 7 in the Supplement). SIRs also typically were higher among individuals after receiving chemotherapy for regional or distant vs localized stage disease, although these differences were statistically significant only for female breast, uterine corpus, ovary, testis, and bladder cancers (eTable 8 in the Supplement).

In absolute risk analyses, EARs were highest (>10 cases per 10 000 person-years) following chemotherapy for peritoneum, small-cell lung, bone, soft tissue, and fallopian tube cancers (Table 1). EARs generally increased with increasing age, exceeding 15 cases per 10 000 person-years among individuals who received a diagnosis at age 65 years or older for several cancers (eTable 7 in the Supplement). Cumulative incidence of tMDS/AML following chemotherapy for first

Figure. Frequency of Medicare Claims for Classes of Chemotherapeutic Agents in Initial Chemotherapy for Patients Diagnosed During 2012-2013, Surveillance, Epidemiology, and End Results (SEER)-Medicare Linked Data



Frequencies were calculated among older adults (aged 66-84 years) who were diagnosed with first primary solid cancer, survived 1 or more years, and received initial chemotherapy, 2012-2013 SEER-Medicare linked data. We ascertained Medicare claims for parenterally administered initial chemotherapy (<12 months following cancer diagnosis), focusing on known leukemogenic agents (alkylating agents, platinum compounds, and topoisomerase II inhibitors; claims codes provided in eTable 4 in the Supplement). SEER-Medicare incompletely captures orally administered agents (eg, cyclophosphamide, temozolomide). "Other specified only" includes any agent listed in eTable 4 in the Supplement other than known leukemogenic agents. eFigure 2 in the Supplement shows trends across the full study period, 2000-2013. eTable 11 in the Supplement provides frequency of claims for specific agents and frequency of unspecified chemotherapy. Additional details regarding SEER-Medicare data also are provided in the eMethods in the Supplement. CNS indicates central nervous system.

primary cancer was low, with the highest estimates (>0.5% at 10 years) for individuals aged 50 years or older at the diagnosis of anus, peritoneum, bone, soft tissue, ovary, fallopian tube, and testis cancers (eTable 9 in the Supplement). Overall survival following tMDS/AML diagnosis was poor (1270 of 1619 patients [78.4%] died; median overall survival, 7 months).

Combining our results with US cancer statistics for the estimated number of cancers diagnosed in 2018,[15] we estimate that nearly 360 000 adults (age, ≥20 years) will have received initial chemotherapy and survived at least one year following diagnosis with one of these 23 cancers during 2018 (eTable 10 in the Supplement). Among these individuals, we conservatively estimate that 521 (73.0%) of the 714 tMDS/AML cases expected to occur within 5 years (ie, by 2023) will be attributable to chemotherapy, with the remaining cases arising owing to various other causes (eg, radiotherapy, genetic susceptibility, or other risk factors, although the cause of most de novo leukemias is unknown).[16]

SEER-Medicare Data: Patterns of Chemotherapy Use

We identified 477 688 older adults (age, 66-84 years) with a diagnosis of first primary solid cancer during 2000-2013 in the SEER-Medicare databases (eTable 3 in the Supplement). A total of 165 820 patients (34.7%) received initial chemotherapy, a proportion that increased slightly during the study period from 31% in 2000-2001 to 38% in 2012-2013 (eFigure 1 in the Supplement shows proportions by year and first primary type). Among patients treated with initial chemotherapy, the proportion with claims for a known leukemogenic agent (alkylating agent, platinum compound, or topoisomerase II inhibitor) increased from 57% in 2000-2001 to 81% in 2012-2013. Platinum compounds drove this increase, rising from 35% in 2000-2001 to 59% in 2012-2013. In contrast, use of alkylating agents remained stable (approximately 21%), and topoisomerase II inhibitors declined slightly (20% in 2000-2001 to 12% in 2012-2013).

In analyses by first primary cancer, platinum compound claims for initial chemotherapy increased most strikingly during the study period for gastrointestinal tract cancers, including esophagus (63% in 2000-2001 to 95% in 2012-2013; most commonly, carboplatin), stomach (29% in 2000-2001 to 78% in 2012-2013; carboplatin and oxaliplatin), colon (1% in 2000-2001 to 77% in 2012-2013; oxaliplatin), and rectum (1% in 2000-2001 to 60% in 2012-2013; oxaliplatin) (the **Figure** shows data for 2012-2013; eFigure 2 in the Supplement shows changes during 2000-2013; eTable 11 in the Supplement provides frequency of claims for specific agents). In addition to these gastrointestinal cancers, in 2012-2013, platinum compounds also were used for most patients receiving initial chemotherapy for oral cavity or pharynx (72%; most commonly, cisplatin), peritoneum (96%; carboplatin), larynx (68%; cisplatin), small-cell lung (97%; carboplatin with etoposide), non-small cell lung

(91%; carboplatin), cervix (96%; cisplatin), uterine corpus (93%; carboplatin), ovary (97%; carboplatin), vagina or vulva (82%; cisplatin), and fallopian tube (97%; carboplatin) cancers.

For certain other cancers, most patients had Medicare claims for known leukemogenic agents as part of initial chemotherapy, most frequently alkylating agents and/or topoisomerase II inhibitors. These cancers included anus (most commonly, mitomycin), liver (doxorubicin), female breast (cyclophosphamide with or without doxorubicin), and bladder (mitomycin). In contrast, fewer than half of the patients receiving initial chemotherapy for soft tissue, pancreas, and brain or central nervous system cancers during 2012-2013 had a claim for a leukemogenic agent, although some misclassification may occur because of underascertainment of specific agents, particularly orally administered agents (eg, temozolomide for brain and/or central nervous system cancer). Increases in claims for other specific agents (without claims for known leukemogenic agents) during the study period were observed for oral cavity/pharynx (most commonly, cetuximab), larynx (cetuximab), soft tissue (gemcitabine), breast (trastuzumab), and brain (bevacizumab) cancers.

Discussion

Based on large-scale, population-based SEER cancer registry data, we found increased tMDS/AML risks following chemotherapy for 22 of 23 solid cancer types (all except colon) diagnosed during 2000-2013 in the United States. These findings suggest a substantial expansion in the patients at risk for tMDS/AML because, in the past, excess risks were established only after chemotherapy for cancers of the lung, ovary, breast, soft tissue, testis, and brain or central nervous system.[2,17] Compared with the only other similarly designed study, which included patients who were diagnosed with the first primary cancer during 1975-2008,[17] our current analyses extend follow-up to 2014, more than double the number of solid cancer patients treated with chemotherapy and more than triple the number of tAML cases, and include tMDS, which became reportable to SEER only in 2001. Based on SEER-Medicare data, we found that the proportion of patients treated with a known leukemogenic agent (alkylating agent, platinum compound, or topoisomerase II inhibitor) increased from 57% during 2000-2001 to 81% in 2012-2013, with platinum compounds explaining much of this increase, although our analysis could not directly estimate tMDS/AML risk associated with these drugs.

Our results provide what we believe to be the first clear evidence of excess tMDS/AML risks following chemotherapy for oral cavity or pharynx, esophagus, stomach, rectum, larynx, bone, cervix, uterine corpus, and vagina or vulva cancers, with risk estimates based on 14 or more tMDS/AML cases after each first primary cancer except the vagina or vulva. For each of these sites, platinum compounds have been introduced to improve outcomes.[18-28] In contrast, excess risks of tMDS/AML have been established for testis, small cell and non-small cell lung, and ovarian cancers, which have been treated with platinum compounds for several decades.[2,3,29] Our large sample size also enabled detection of excess tMDS/AML risks for the first time after the rare peritoneum and fallopian tube cancers, which generally are treated with platinum compounds, paralleling recommended approaches for ovarian cancer.[30] These results are consistent with known leukemogenicity of platinum compounds, which induce highly cytotoxic DNA intrastrand crosslinks,[2,3,29,31] with particularly high risks after carboplatin.[3,32] In our study, many sites with the highest tMDS/AML SIRs in SEER were most commonly treated with carboplatin based on SEER-Medicare data. In contrast, it is unknown whether the lower SIRs that we observed after rectal and colon cancers reflect lower leukemogenicity of oxaliplatin owing to variation in myelotoxic effects among the different platinum compounds[33,34] or the need for further follow-up because oxaliplatin was not widely used for these cancers until the latter portion of our study period.

Among the remaining first primary cancers we evaluated, we report what we believe to be the novel observation that tMDS/AML risks in SEER are elevated in the modern treatment era following chemotherapy for liver, pancreas, and bladder cancers, and we suggest confirmation of the previous SEER report of elevated tAML risk since 2000 for anal cancer.[17] These risks are consistent with SEER-Medicare descriptive data and literature documenting frequent use of the alkylating agent mitomycin for bladder[35-37] and anal[38-40] cancers and doxorubicin-containing therapy for liver cancer.[41] Elevated tMDS/AML risks after pancreatic cancer could be attributable to platinum compounds, used for more than one-third of patients by 2012-2013 in our data.[42] Finally, we show that the well-established increased tMDS/AML risks persist in the modern era following cytotoxic chemotherapy for female breast, soft tissue, and brain or central nervous system cancers.[2,17] Continued monitoring of the magnitude of these risks is warranted.

The tMDS/AML SIRs were highest for patients treated at younger ages but generally remained significantly elevated for patients treated at ages 65 years or older, whereas tMDS/AML EARs typically increased with increasing age at diagnosis. Studies with cumulative chemotherapy doses are needed to disentangle potential differences in risk by age at exposure based on treatment duration and intensity, comorbidities, or host susceptibility to tMDS/AML,[43] accounting for the rising incidence of MDS/AML with increasing age. The higher tMDS/AML SIRs for more advanced-stage cancer are consistent with more frequent use of leukemogenic agents, longer treatment duration, and/or more subsequent treatment for persistent, progressive, or relapsed disease. The tMDS/AML risks generally persisted 5 years or more following diagnosis; however, our latency results should be interpreted cautiously because SEER lacks data on subsequent chemotherapy. Finally, for certain first primary types, tMDS/AML risks were higher after chemoradiotherapy than chemotherapy alone, which is consistent with previous studies suggesting that radiotherapy contributes somewhat to tMDS/AML risk,[3,29] although the exact magnitude of tMDS/AML risk associated with radiotherapy is controversial.

Limitations

The most important limitations of our SEER-based analysis of tMDS/AML risk are the lack of data on chemotherapy agents and doses for individual patients as well as lack of data on subsequent therapy. The exact magnitude of our risk estimates, including the proportions of excess cases, should therefore be

interpreted cautiously. Heightened surveillance among cancer survivors may account for a fraction of the excess risk that we observed, particularly for MDS, but elevated risks for both tAML and tMDS and well-established leukemogenicity of certain agents argue against this rationale as an explanation for our findings. We also could not directly compare tMDS/AML risks among individuals who did and did not receive initial chemotherapy because receipt of initial chemotherapy is underascertained in SEER; thus, we cannot definitively identify patients who did not receive chemotherapy. Despite these limitations, registry data are useful for assessing tMDS/AML risks because of the large patient population, as demonstrated by a recent meta-analysis of second cancers following cisplatin-containing chemotherapy from 11 clinical trials that included only 2629 patients with 14 tMDS/AML cases.[44]

To help address the lack of detailed chemotherapy data in SEER, we used the SEER-Medicare database to describe population-level treatment practices over the study period. Medicare is largely limited to older adults, who may be less fit for standard therapy; therefore, our estimated percentages of patients receiving any chemotherapy or specific agents likely are conservative (ie, underestimates). Overall, however, the patterns that we observed in Medicare were consistent with documented treatment practices regardless of age. In addition, sensitivity and specificity of Medicare claims are generally high but vary by agent and calendar year,[45] which may have affected some of our estimated changes in clinical practice. Our SEER-Medicare data analysis focused on known leukemogenic agents (platinum compounds, alkylating agents, or topoisomerase II inhibitors). Further studies with dose information are needed to evaluate potential leukemogenicity of other classes of agents, such as taxanes.

Conclusions

We report an increase in the number of patients with elevated risk for developing tMDS/AML after cancer chemotherapy in the modern treatment era. Emphasizing the importance of our findings on a population level, we estimate that nearly 360 000 adults who have survived 1 year or more after a diagnosis of solid cancer in the United States in 2018 will have received initial chemotherapy and nearly three-quarters of the 714 tMDS/AML diagnoses expected by the year 2023 among these patients could be attributable to chemotherapy. This proportion would be expected to be even higher among those receiving known leukemogenic agents. Although the absolute risk of developing tMDS/AML is low, its treatment is often resource intensive and associated with substantial morbidity; overall survival is poor, highlighting its clinical significance. Treatment risk and benefit assessments should balance tMDS/AML risks and other chemotherapy-related adverse effects against potential gains in survival, particularly for patients with a favorable prognosis. Continued efforts to develop effective and less toxic chemotherapeutic approaches are needed.[32,46]

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Author Affiliations: Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland (Morton, Dores, Schonfeld, Linet, Sigel, Curtis); Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland (Lam); Human Genetics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland (Tucker).

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