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Therapy-related myeloid leukemia after treatment for epithelial ovarian carcinoma: An epidemiological analysis

Agnieszka Vay [a,*], Sanjeev Kumar [b], Shelly Seward [a], Assaad Semaan [a], Charles A. Schiffer [c], Adnan R. Munkarah [a,d], Robert T. Morris [a]

[a] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Wayne State University, Detroit, MI 48201, USA
[b] Department of Gynecologic Oncology, Mayo Clinic, Rochester, MN 55905, USA
[c] Department of Medicine and Oncology, Wayne State University, Detroit, MI 48201, USA
[d] Department of Women's Health Services, Henry Ford Health Systems, Detroit, MI 48202, USA

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ABSTRACT

Objective. Therapy related acute myeloid leukemia (t-AML) is a potential late complication of cytotoxic therapy, and it is of particular concern in the treatment of patients with epithelial ovarian carcinoma (EOC) exposed to multiple courses of chemotherapy during the course of their disease. This study examines the incidence, characteristics and clinical outcomes of patients who developed secondary myeloid-type leukemia after a diagnosis of EOC.

Methods. National Cancer Institute's Surveillance, Epidemiology and End Results database was pooled for diagnosis of secondary myeloid leukemia after an initial diagnosis of EOC. This group of patients was compared to patients with *de novo* AML, and to EOC patients who did not develop secondary myeloid leukemia. Demographic, cytopathological and survival data were recorded. Cox Proportional Hazards model was used to calculate hazard ratios (HR) for developing secondary leukemia and to determine the statistically significant variables impacting survival. Kaplan–Meier estimates of survival were obtained and comparisons between the groups were performed using log-rank test.

Results. One hundred and nine myeloid leukemia cases were identified among 63,359 patients with a prior diagnosis of EOC for an overall incidence of 0.17%. The median latency to development of leukemia was 4 years (range 0–27 years). Median survival from the time of secondary leukemia diagnosis was 3 months and significantly worse than the 6 month median survival in patients with *de novo* AML ($p<0.001$). Age at leukemia diagnosis greater than 65 and development of secondary *vs. de novo* leukemia had a statistically worse prognosis on multivariate analysis (HR of 2.69, 95%CI 2.60–2.78 and 1.81, 95%CI 1.49–2.20 respectively). The development of secondary leukemia was more common with EOC diagnosis made prior to the platinum/taxane era (HR 6.70, 95%CI 3.69–12.18). There was no difference in median survival between EOC patients who developed AML and those who did not.

Conclusion. Development of t-AML is a rare but lethal event among EOC patients, and its incidence has decreased significantly since the use of platinum/taxane-based chemotherapy became the standard of care.

Introduction

Therapy related myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (t-AML) have been described as late complications of cytotoxic chemotherapy [1]. Although a direct mechanism of causality remains to be elucidated, a variety of cytotoxic agents have been implicated in the development of t-MDS/t-AML with variable latencies [1]. Historically t-MDS/t-AML carries a worse prognosis when compared to the *de novo* AML, most likely as a result of unfavorable cytogenetics [1].

Epithelial ovarian carcinoma (EOC) has the highest mortality rate among all gynecological cancers, with US annual disease related deaths exceeding all other gynecological cancer deaths combined. Despite most patients initially presenting with extensive bulky disease, the relative sensitivity of these cancers to chemotherapy has enabled the median survival to approach 5 years [2]. The majority of patients require initial adjuvant chemotherapy after cytoreductive surgery, and frequently numerous courses of cytotoxic treatment upon subsequent relapses [3]. With rising interest in maintenance and consolidation trials [4], as well as the use of targeted therapies, such as PARP inhibitors which may predispose to further DNA damage, additional exposures to cytotoxic agents are to be anticipated. This prolonged use of cytotoxic therapy raises the issue of potentially increasing the risk of therapy-induced myelodysplastic syndromes. Several series

* Corresponding author. Fax: +1 313 993 8857.
E-mail address: agnivay@gmail.com (A. Vay).

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and case reports describe t-MDS/t-AML after treatment for ovarian cancer, but to date there has been no large series looking at patient characteristics and evaluating outcomes with this entity [5–9]. The largest case–control study of secondary leukemia in ovarian cancer patients showed decreased relative risk with the use of platinum compounds *vs*. traditional alkylating agents, but did not encompass any patients treated with taxanes [9]. To better understand the risks of therapy-induced myelodysplasia after treatment for ovarian cancer and improve patient counseling, we examined the incidence, characteristics and clinical outcomes of patients who developed secondary myeloid-type leukemia after a diagnosis of ovarian cancer based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.

Materials and methods

The study was deemed exempt by the institutional review board at Wayne State University/Karmanos Cancer Center. Subjects with the diagnosis of secondary myeloid leukemia following a diagnosis of primary ovarian cancer were identified using the SEER database from 1973 to 2006. The patients thus identified were compared first to a group of patients who developed *de novo* AML without history of prior cancer diagnosis, and second to patients with ovarian cancer who did not develop a secondary malignancy. Eligibility criteria included diagnosis of EOC with or without subsequent development of myeloid type leukemia, and adult patients with primary AML. Patients with multiple primary cancers other than myeloid leukemia and ovarian cancer, ovarian cancer histology other than epithelial and pediatric patients (<18 years old) at the time of diagnosis of either malignancy were excluded. Demographic parameters abstracted included age at each cancer diagnosis, race, dates of ovarian cancer and leukemia diagnosis, and marital status. Cytopathological data recorded included initial method of diagnosis, stage, grade, and histology of each disease entity. Stage was further classified as early (defined as local disease) or advanced (defined as regional/distant disease). Therapeutic modalities directed at ovarian cancer were obtained. Vital status was recorded and survival was calculated as the number of months from the diagnosis of a specific disease to the time of death or last follow-up. Thus, ovarian cancer-specific survival was calculated from the time of diagnosis of the ovarian neoplasm, while leukemia-specific survival was calculated from the onset of leukemia diagnosis. Year of diagnosis of ovarian cancer was further stratified as prior to or after 1982, when the use of platinum-based chemotherapy became standard of care, and prior to or after 1996, when paclitaxel supplanted cyclophosphamide in the treatment regimes. This categorization was considered to delineate whether the use of platinum or taxane agents had an impact on secondary leukemia incidence and overall prognosis. Patients were further subdivided into age greater than or less than 65 years.

All statistical analyses were carried out using SPSS 19.0. Frequency distributions between the demographic data were calculated using X^2 test. Hazard ratios for risk of secondary leukemia development among EOC patients were derived using Cox regression. Survival between the therapy-induced and *de novo* leukemia groups was calculated using Cox Proportional Hazards model, controlling for other predictor variables such as patient age, race, marital status, disease stage, grade and treatment modality. Survival tables were generated using Kaplan–Meier estimates, with log-rank test used for comparisons between the groups. Significant p values were defined as <0.05.

Results

A total of 270 secondary hematologic malignancies were identified among 63,520 patients with a prior diagnosis of primary EOC, and 109 of the above included myeloid-type leukemias. Acute myeloid leukemia accounted for the majority of cases (n = 98), and CML was rare (n = 11). Thus, the calculated incidence of secondary myeloid malignancies among patients with a prior ovarian cancer diagnosis was 0.17%.

The characteristics of the ovarian cancer cohort that developed secondary leukemia are listed in Table 1. The majority of ovarian cancers patients presented at advanced stage, with poorly differentiated histology, and were initially treated surgically, while only a minority received radiation therapy. Forty-eight percent of patients who developed secondary leukemia had their ovarian cancer diagnosed after 1982, at a time when platinum based chemotherapy became standard of care in the management of ovarian neoplasms. In contrast only 14% of patients with secondary leukemia had their initial EOC diagnosis made after 1996. The mean and median latency time between the diagnosis of EOC and the development of leukemia was 5 and 4 years respectively (interval 0–27 years). In patients with early stage EOC median latency to leukemia onset was significantly longer than in advanced stage (4 *vs*. 3 years, $p = 0.04$).

In patients who developed secondary leukemia after EOC there was no statistically significant difference in survival from the time of ovarian cancer or leukemia diagnosis based on histological grade of the ovarian cancer, history of surgical or radiation treatment, race, or marital status. As expected, we found that ovarian cancer stage and age at the time of leukemia diagnosis were significant prognostic variables affecting survival from the time of ovarian cancer diagnosis on univariate analysis. Predictors of leukemia associated mortality, calculated from the time of secondary leukemia onset, included ovarian cancer stage, and type of leukemia (CML *vs*. AML). The median survival estimates for these independent variables are depicted in Table 1. When Cox Proportional Hazards model was

Table 1
Characteristics of EOC cases developing secondary myeloid leukemia and their impact on ovarian cancer and leukemia specific survival.

Variable	n (%)	Median ovarian cancer survival (months)	*P*	Median leukemia survival (months)	*P*
Ovarian cancer stage					
Early	31 (28.4)	73	0.025	5	0.042
Late	73 (67.0)	44		3	
Unknown	5 (4.6)	59		2	
Ovarian cancer grade					
1	13 (11.9)	64	0.838	3	0.392
2	12 (11.0)	48		2	
3	37 (34.1)	47		3	
Unknown	47 (43)	48		3	
Surgical treatment					
Yes	97 (89.0)	52	0.102	3	0.317
No	9 (8.3)	48		2	
Unknown	3 (2.7)	39		3	
Radiation treatment					
Yes	10 (8.3)	44	0.546	2	0.205
No	99 (91.7)	49		3	
Age at leukemia diagnosis					
<65	69 (63.3)	59	<0.001	3	0.122
65 or older	40 (36.7)	36		3	
Year of ovarian cancer diagnosis					
Prior to 1982	57 (52.3)	56	0.375	2	0.068
1982–1995	37 (33.9)	44		3	
1996 onward	15 (13.8)	48		4	
Race					
White	100 (91.7)	48	0.696	3	0.597
African American	6 (5.5)	64		2	
Other	3 (2.8)	56		2	
Marital status					
Single	7 (6.4)	72	0.148	2	0.275
Married	72 (66.1)	53		3	
Divorced/widowed	30 (27.5)	46		4	
Leukemia type					
AML	98 (89.9)	49	0.137	3	0.003
CML	11 (10.1)	81		12	

performed on the statistically significant variables, advanced age at leukemia diagnosis carried poor prognosis for ovarian cancer survival with a HR of 1.79 (95%CI 1.13–2.84) and development of CML *vs*. AML was associated with improved leukemia survival with HR of 0.36 (95% CI 0.18–0.73). Stage was not an independent predictor for either ovarian cancer or leukemia specific survival with advanced stage carrying a HR of 0.96 (95%CI 0.59–1.57) for ovarian cancer survival and a HR of 1.51 (95%CI 0.56–4.04) for leukemia survival. However, in the secondary leukemia cohort, patients with early stage EOC had significantly shorter median survival from the time of ovarian cancer diagnosis than their early stage counterparts who did not go on to develop secondary leukemia (73 *vs*. 279 months respectively, $p<0.001$), indicating that the development of leukemia was a terminal event in patients who would have otherwise been long term survivors of EOC.

The patients with secondary leukemia were then compared to 22,803 adult patients identified in the database with a diagnosis of *de novo* AML. Patients with secondary leukemia were slightly older with mean age at leukemia diagnosis of 65.2 *vs*. 63.1, but this difference did not reach statistical significance ($p=0.23$). Race and marital status were also well balanced between the groups, with the majority of patients being white. Median survival from the time of secondary leukemia diagnosis among ovarian cancer patients was 3 months (95%CI 2.3–3.7), and significantly worse than the 6 months median survival (95%CI 5.8–6.2) in patients with primary leukemia ($p<0.001$). When the eleven secondary CML cases were excluded from the analysis, the median leukemia-specific survival in patients with secondary leukemia was unchanged. On multivariate analysis, leukemia as a second event (HR 1.81, 95%CI 1.49–2.20) and age at leukemia diagnosis >65 (HR 2.69, 95%CI 2.60–2.78) were significant independent predictors of poor prognosis in the entire leukemia cohort.

Finally, the patients with ovarian cancer who developed secondary myeloid malignancy were compared to 63,250 EOC patients who did not. Patients who developed secondary leukemia were significantly younger, and were more likely to have had surgical debulking, radiation treatment, and early stage and well-differentiated disease, as depicted in Table 2. The calculated incidence of secondary leukemia among patients diagnosed with EOC before 1982 was 6/1000, compared to 2/1000 for patients diagnosed during the time period between 1982 and 1996, and 0.4/1000 following an EOC diagnosis made after 1996. When the impact of patient characteristics on risk of leukemia development was analyzed using Cox regression, the era of ovarian cancer diagnosis was the most significant factor. Patients diagnosed with ovarian cancer prior to 1982 had a HR of 6.70 (95%CI 3.69–12.18) of developing secondary leukemia when compared to patients diagnosed with EOC after 1996, and a HR of 2.74 (95%CI 1.51–4.98) for patients diagnosed with EOC between 1982 and 1995. These results are demonstrated in Table 3. Advanced age at ovarian cancer diagnosis and undergoing surgical treatment were other significant factors associated with secondary leukemia.

After a median follow-up time of 21 months no statistically significant difference was seen in survival between the two EOC groups, despite median survival of 28 months observed for EOC without subsequent malignancy *vs*. 49 months for patients with EOC followed by secondary leukemia ($p=0.54$), as shown in Fig. 1. The calculated 2, 4 and 6 year survival for the secondary leukemia group was 53%, 34% and 2% respectively. In contrast the 2, 4, and 6 year survival in EOC patients who did not develop leukemia was 38%, 31% and 15% respectively, with all the differences statistically significant between the two groups ($p<0.001$ for all time frame comparisons). The HRs were calculated at 2, 4, 6, and 8 years after EOC diagnosis for patients who developed secondary leukemia. The two year survival was statistically more favorable in the secondary leukemia cohort when compared to the remainder of EOC patients (HR 0.17, 95%CI 0.09–0.30) but this difference disappeared at 4 and 6 years, and the trend actually reversed at 8 years when a significantly worse survival was observed among these patients (HR 1.83, 95%CI 1.18–2.84). When stratified by EOC stage, the median ovarian cancer survival was shorter in patients with early stage disease with secondary leukemia than those with no secondary malignancy (73 *vs*. 279 months, $p<0.001$). On the other hand, patients with advanced stage disease who had longer median ovarian cancer survival (42 *vs*. 21 months, $p=0.05$). were more likely to develop secondary leukemia, indicating that patients with more aggressive forms of EOC simply did not survive long enough or were not exposed to sufficient treatment to develop a secondary malignancy. Multivariable analysis confirmed

Table 2
Comparison of patient characteristics among ovarian cancer cases whose ovarian cancer was the only primary and those who developed secondary myeloid malignancy.

	Developed leukemia		
	Yes	No	*p*
	n (%)	n (%)	
Age at diagnosis			
Younger than 65	69 (63.3%)	33,879 (53.6%)	0.026
65 or older	40 (36.7%)	29,371 (46.4%)	
Year of diagnosis			
Before 1982	57 (52.3%)	9817 (15.5%)	<0.001
1982–1995	37 (33.9%)	20,096 (31.8%)	
1996 onward	15 (13.8%)	33,337 (52.7%)	
Surgical treatment			
Yes	96 (88.1%)	47,993 (75.9%)	0.008
No	13 (11.9%)	13,742 (21.7%)	
Unknown	0	1515 (2.4%)	
Radiation treatment			
Yes	9 (8.3%)	2259 (3.6%)	0.017
No	100 (91.7%)	60,991 (96.4%)	
Stage			
Unknown	5 (4.6%)	3802 (6%)	0.009
Early	31 (28.4%)	10,991 (17.4%)	
Advanced	73 (67%)	48,457 (76.6%)	
Grade/differentiation			
1	14 (12.8%)	4401 (7%)	0.037
2	11 (10.2%)	9266 (14.6%)	
3	37 (33.9%)	25,160 (39.8%)	
Unknown	47 (43.1%)	24,423 (38.6%)	
Race			
White	100 (91.7%)	55,306 (87.4%)	0.446
African American	6 (5.5%)	3868 (6.1%)	
Other	3 (2.8%)	3875 (6.1%)	
Unknown	0	201 (0.4%)	

Table 3
Cox Proportional Hazards model of factors associated with development of secondary leukemia among EOC patients.

	HR	95%CI
Age at diagnosis		
Younger than 65	1.00	
65 and older	1.56	1.04–2.34
Race		
White	1.00	
African American	1.13	0.50–2.58
Other	0.49	0.16–1.55
Stage		
Early	0.60	0.23–1.56
Advanced	1.00	
Tumor grade		
1	0.89	0.56–1.42
2	0.80	0.41–1.53
3	1.00	
Surgical debulking		
Yes	2.65	1.47–4.79
No	1.00	
Radiation treatment		
Yes	1.45	0.71–2.96
No	1.00	
Year of diagnosis		
Before 1982	6.70	3.69–12.18
1982–1995	2.74	1.51–4.98
1996 onward	1.00	

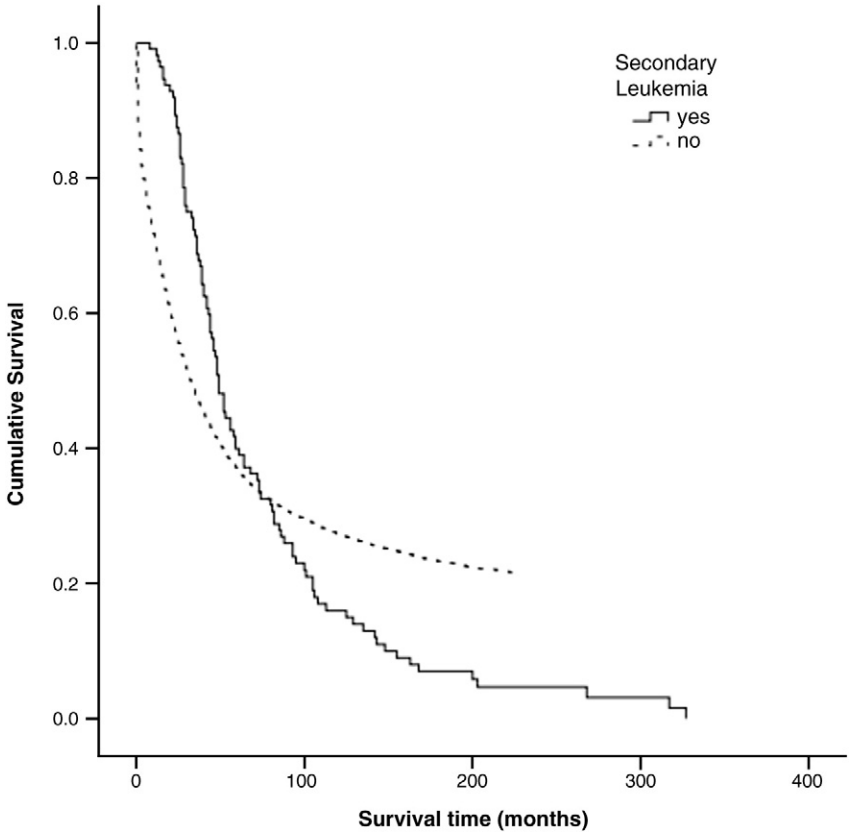

Fig. 1. Survival of EOC patients who developed secondary myeloid leukemia *vs*. those with no secondary malignancies.

that for the entire EOC cohort younger age at diagnosis, non-African American race, early stage/well-differentiated disease, surgical debulking and EOC diagnosis made after 1982/1996 were important predictors of improved survival.

Discussion

This study is the largest to date on the outcomes of patients who develop t-MDS/t-AML after a prior diagnosis of EOC. The results of our analysis suggest that development of secondary myeloid malignancy is a rare event among patients with a history of ovarian cancer, and that the secondary leukemia-specific median survival of 3 months is significantly worse than survival of patients with *de novo* AML. These findings are consistent with the previously accepted notion that patients with t-MDS/t-AML have a grave prognosis [1].

Multivariable analysis revealed that aside from the type of leukemia (chronic *vs*. acute), the most important prognostic factor affecting leukemia-specific survival among patients with both *de novo* and secondary myeloid leukemia was advanced age at leukemia diagnosis with patients older than 65 years having increased risk of dying from the disease. This is not surprising as older patients may not be candidates for more aggressive treatments given their performance status and other medical comorbidities, and that these comorbidities affect overall survival by themselves [10].

As anticipated, epithelial ovarian cancer patients with prolonged survival were at risk for developing leukemia. This is substantiated by the observation that patients who developed secondary leukemia had more favorable characteristics such as younger age, early stage/well-differentiated disease, and greater frequency of surgical intervention, when compared to the EOC patients who did not have a secondary malignancy. Even among patients with advanced stage EOC, the median survival was higher in the group that went on to develop secondary leukemia, suggesting that the patients with highly aggressive ovarian cancer do not survive long enough to develop secondary malignancies such as t-AML. In addition, patients with longer survival are more likely to be exposed to repeat cytotoxic treatments throughout their lifetime.

Despite the lack of information on chemotherapy administration in the database, it is worth noting that after multivariable analysis, the year of EOC diagnosis was the most important factor affecting the incidence of secondary leukemia. The incidence was lowered threefold when diagnosis of EOC was made between 1982 and 1995 when compared to the period prior to 1982, and further lowered 15-fold in the mid 1990s. It is reasonable to infer that when platinum therapy became the standard in adjuvant first-line treatment of EOC in the early 1980s and subsequently platinum/taxane based treatment supplanted platinum/cyclophosphamide in the mid 1990s [11], the overall risk of developing secondary leukemia has substantially decreased. This supports the previously reported notion that traditional alkylating agents, now rarely used in the treatment of EOC, have a higher leukemogenic potential than the current standard of care [1,9,12]. It has been shown in a previous case–control study of ovarian cancer patients that the use of melphalan carried a relative risk of developing secondary leukemia of 20.8 (95%CI 6.3–68.3) as compared to that of the platinum agents of 4.0 (95%CI 1.4–11.4), however the study did not include any patients treated with the taxanes [9]. Thus a major finding of our study remains that a substantial decrease in the secondary leukemia incidence was observed since the advent of the taxane era. This observed decrease in t-AML incidence certainly offsets a potential increase previously reported with carboplatin in comparison to cisplatin (RR of 6.5, 95%CI 1.2–36.6 *vs*. RR of 3.3, 95%CI 1.1–9.4 respectively) [9] since carboplatin is often substituted for cisplatin in the front line therapy of EOC [13]. Radiation treatment, while more prevalent in the secondary leukemia cohort is rarely used

in the setting of ovarian cancer and the analysis did not show a significant effect of radiation treatment on leukemia development.

As anticipated advanced age, stage and grade, as well as African American race were negative prognostic variables for ovarian cancer specific survival, while surgical treatment carried a favorable prognosis among patients with EOC. For EOC patients who developed leukemia these factors failed to reach statistical significance for both ovarian and leukemia associated survival, with stage being significant only on univariate analysis. This is expected in light of very short survival once secondary leukemia is diagnosed — therefore among this cohort of long term ovarian cancer survivors once secondary leukemia develops, favorable EOC prognostic factors no longer impact further survival. Patients with early stage EOC who developed leukemia had significantly worse survival than their counterparts without secondary malignancy further supporting this notion. Although there was no statistically significant difference in overall survival between EOC patients who developed secondary leukemia and those who did not, comparison of their 2, 4 and 6 year survivals indicates that patients developing secondary leukemia clearly experience a different course of disease from the time of their EOC diagnosis. The development of secondary leukemia in these patients leaves virtually no long-term survivors, in comparison to the entire EOC cohort, where approximately 15% of patients are alive at the time of last follow-up. While the HR for survival at 2 years after EOC diagnosis is more favorable in the EOC patients who go on to develop secondary leukemia, this favorable trend is reversed 8 years after their EOC diagnosis. The survival curves cross at 70 months after EOC diagnosis, which roughly corresponds to the mean latency time between EOC diagnosis and leukemia development reported in this study (Fig. 1). It is further possible that before the development of t-MDS/t-AML some of these patients may have been cured from their EOC.

Aside from the lack of data on ovarian cancer status at the time of death from leukemia and previously mentioned chemotherapy specifics, other limitations of the study include its retrospective nature, lack of centralized pathology review, large number of ovarian cancer cases with unknown degree of differentiation, possible coding misclassifications of recorded parameters, and lack of documentation on the use of hematopoietic support factors, which may also contribute to malignant transformation and affect patient outcomes [14,15]. In addition, our database search was limited to myeloid leukemias, and did not specifically include myelodysplastic syndrome, which may have led to underestimation of the total incidence of myelodysplasia. However, World Health Organization no longer distinguishes the two entities as separate diseases, and the majority of myelodysplastic syndromes progress to fulminant t-AML [6], which leads us to believe that we captured the majority of t-MDS/t-AML.

In conclusion, this large study shows that the risk of developing t-MDS/t-AML after a diagnosis of EOC is low. Furthermore, the incidence is dependent on the era of EOC diagnosis, with decreased frequency of t-MDS/t-AML noted since the use of platinum/taxane based regimens became standard of care in the treatment of EOC. With a median survival of 3 months and essentially no long-term survivors in the secondary leukemia group, the prognosis is uniformly poor. Thus development of secondary leukemia can be regarded as a preterminal event in this patient population. The results of this study can be very valuable when counseling EOC patients regarding their risk of developing t-MDS/t-AML. Further studies and follow-up are needed to establish that maintenance regimens and targeted therapies, such as PARP inhibitors which may cause additional DNA damage, lead to similar outcomes.

Conflict of interest statement

The authors have no financial interests or other competing interests to disclose.

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