Analysis of Secondary Leukemia and Myelodysplastic Syndrome After Chemotherapy for Solid Organ Tumors Using the Food and Drug Administration Adverse Event Reporting System (FAERS)

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ABSTRACT – Purpose: As the prognosis of cancer patients deteriorates, secondary carcinogenesis after chemotherapy, especially secondary hematological malignancies, becomes a serious problem. However, information on the frequency and time of onset of secondary hematological malignancies and the risk of hematological malignancy with different drugs is scarce. This study aimed to evaluate the incidence of leukemia and myelodysplastic syndrome in patients with solid tumors, including breast, colon, gastric, pancreatic, small cell lung, non-small cell lung, esophageal, ovarian, cervical, and endometrial cancers. **Methods:** Using the United States Food and Drug Administration Adverse Event Reporting System, we analyzed the reporting rates, reporting odds ratios, and the reporting onset times of secondary leukemia and myelodysplastic syndrome for each drug used. **Results**: The leukemia reporting rates were higher in breast, small cell lung, ovarian, and endometrial cancers than in other cancers, and the myelodysplastic syndrome reporting rates were higher in ovarian and endometrial cancers than in other cancers. For each cancer type, the reporting odds ratios of cytocidal anticancer agents, such as taxanes, anthracyclines, alkylating agents, platinum, and topoisomerase inhibitors, were higher than those of other drugs. Alternatively, the reporting odds ratios of molecular targeted drugs and immune checkpoint inhibitors were not higher than those of other drugs. Approximately half of the cases of leukemia and myelodysplastic syndrome were reported within 1 to 4 years after chemotherapy. **Conclusions:** Our study clarified the risks of leukemia and myelodysplastic syndrome for several anticancer drugs in patients with solid tumors. Our data may aid in the assessment of the risks of secondary leukemia and myelodysplastic syndrome when medical oncologists, clinical pharmacists, and patients select chemotherapy regimens.

INTRODUCTION

Although the development of chemotherapy has prolonged the life expectancy of cancer patients, secondary cancers, especially therapy-related myeloid neoplasms (t-MNs), are a serious problem (1,2). Many reports have indicated that breast cancer patients are at a high risk of marrow neoplasms after chemotherapy (3-5) and that treatment for Hodgkin's lymphoma is a risk factor for leukemia (6). However, these reports were limited to cancer type and specific anticancer drugs, and there exists little comprehensive information on the extent to which each anticancer drug increased the risk for t-MN, including leukemia and myelodysplastic syndrome (MDS), in each cancer type. Therefore, medical oncologists, clinical pharmacists, and patients have not been able to adequately consider the risk of t-MN when selecting chemotherapy regimens.

Large-scale health information databases are beginning to be used in drug discovery and development. The US Food and Drug Administration Adverse Event Reporting System (FAERS) has registered more than three million spontaneous reports of adverse events (7) and is an effective tool for comprehensive risk assessments of adverse drug events.

In this study, we successfully conducted a comprehensive survey and analyzed the reporting frequency and the time to the onset of leukemia and MDS and the risk of leukemia and MDS for different drugs in patients with different solid tumors using

reports from FAERS.

ABBREVIATION. t-MN: therapy-related myeloid neoplasm; MDS: myelodysplastic syndrome; FAERS: US Food and Drug Administration Adverse Event Reporting System; AML: acute myeloid leukemia; ROR: reporting odds ratio; CI: confidence interval

METHODS

Of the 11,289,189 adverse event reports from FAERS from 1997 to the second quarter of 2019, cases of breast (77,096 reports), colon (11,499 reports), gastric (6,866 reports), pancreatic (12,368 reports), small cell lung (3,625 reports), non-small cell lung (36,930 reports), esophageal (3,409 reports), ovarian (19,402 reports), cervical (1,818 reports), and endometrial (1,319 reports) cancers were included in this study. The report data were extracted using CzeekV Pro (version 5.0.12, INTAGE Healthcare Inc., Tokyo, Japan, accessed September 2019). Reports of adverse events containing the word "leukemia" were considered leukemia reports; thus, the leukemia reports included acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphoblastic leukemia, and acute myeloid leukemia (AML). We investigated the reporting rates, reporting odds ratios (RORs), and the times to onset of leukemia and MDS reported as adverse events after anticancer drug use in the reports of each cancer type. The RORs and 95% confidence intervals (CIs) were calculated using Eq. (8).

$$\mathrm{ROR} = \frac{n11 / n21}{n12 / n22} \quad (1)$$

$$95\%\ \mathrm{CI} = \exp\left[\log(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{n11} + \frac{1}{n12} + \frac{1}{n21} + \frac{1}{n22}}\right] \quad (2)$$

In these formulas, n11 refers to patients who used an anticancer drug and reported a hematological malignancy, such as leukemia or MDS; n12 refers to patients who used an anticancer drug but did not report a hematological malignancy; n21 refers to patients who did not use an anticancer drug but reported a hematological malignancy; and n22 refers to patients who did not use an anticancer drug and did not report a hematological malignancy. We excluded reports without information regarding the onset time of leukemia or MDS from the analysis. Statistical analysis was performed using a chi-square test (StatView; Abacus Concepts, Berkeley, California, USA). Statistical significance was set at $P<0.05$. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Reporting rates of leukemia and MDS

Reports of leukemia accounted for 0.07-1.06% of all reports of adverse effects for each cancer type (Figure 1A). The reporting rates of leukemia were high in endometrial (1.06%), small cell lung (1.02%), ovarian (1.02%), and breast (0.90%) cancers. Conversely, there are few reports of leukemia in colorectal (0.07%), pancreatic (0.11%), and non-small cell lung (0.12%) cancers.

Reports of MDS accounted for 0.08-0.83% of all reports of adverse effects for each cancer type (Figure 1B). The reporting rates of MDS were high in endometrial (0.83%) and ovarian (0.62%) cancers. Conversely, there are few reports of MDS in colorectal (0.06%), pancreatic (0.08%), gastric (0.10%), and non-small cell lung (0.11%) cancers.

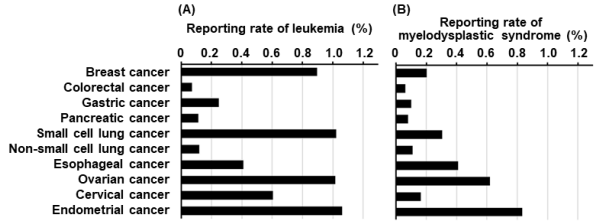

Figure 1. Reporting rates of leukemia (A) and myelodysplastic syndrome (MDS) (B).

RORs of leukemia in breast cancer

The RORs for docetaxel, paclitaxel, doxorubicin, epirubicin, cyclophosphamide, fluorouracil, methotrexate, and tamoxifen were greater than one (Figure 2). For patients on cyclophosphamide, fluorouracil, methotrexate, and doxorubicin, the RORs (95% CIs) were 11.89 (10.09-13.96), 10.48 (8.97-12.25), 9.62 (7.56-12.24), and 6.11 (5.21-7.16), respectively, and the reporting rates were 3.81%, 5.75%, 7.23%, and 3.76%, respectively. The RORs for capecitabine, exemestane, fulvestrant, trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine, neratinib, palbociclib, and bevacizumab were less than one.

RORs of leukemia in small cell lung cancer

The ROR (95% CI) of etoposide, a topoisomerase inhibitor, was 3.68 (1.73–7.83), and the reporting rate in patients on etoposide was 1.68% (Figure 3). There were no reports of leukemia in patients receiving nivolumab or ipilimumab, which are immune checkpoint inhibitors ($P<0.05$).

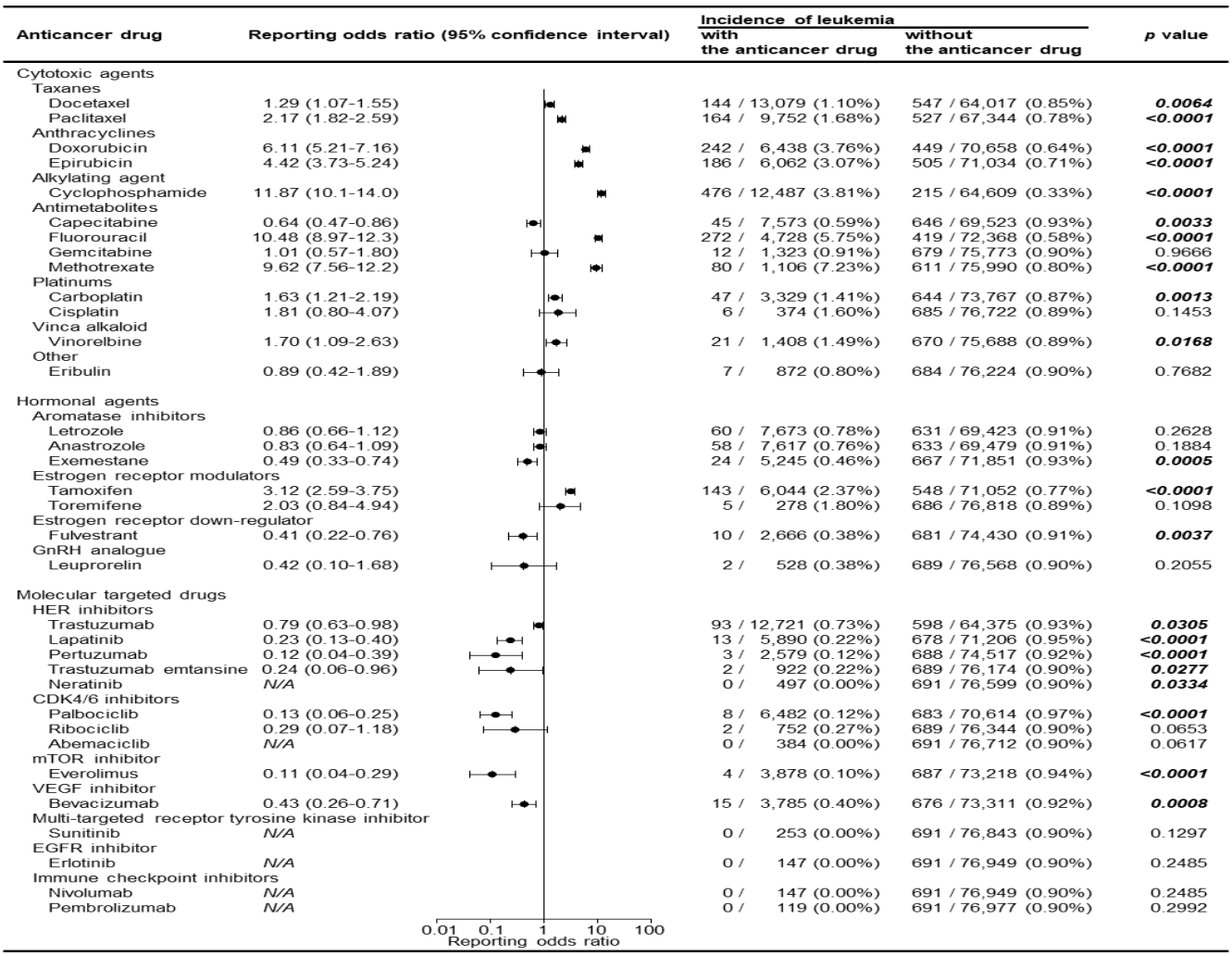

Figure 2. Reporting odds ratios for leukemia in breast cancer. GnRH: gonadotropin releasing hormone, HER: human epidermal growth factor receptor, CDK4/6: cyclin-dependent kinase 4/6, mTOR: mammalian target of rapamycin, VEGF: vascular endothelial growth factor, EGFR: epidermal growth factor receptor.

RORs of leukemia and MDS in ovarian cancer

For leukemia, the RORs for carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin, gemcitabine, etoposide, irinotecan, cyclophosphamide, trabectedin, and olaparib were greater than one (Figure 4). In patients receiving cyclophosphamide, etoposide, and irinotecan, the RORs (95% CI) were 11.40 (7.76–16.75), 11.17 (6.96–17.93), and 10.87 (5.58–21.20), respectively, and the reporting rates were 8.97%, 9.38%, and 9.62%, respectively. The RORs of niraparib and rucaparib were less than one.

For MDS, the RORs for carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin, etoposide, irinotecan, cyclophosphamide, and olaparib were greater than one (Figure 5). In patients on irinotecan and cyclophosphamide, the RORs (95% CI) were 18.56 (9.42–36.57) and 11.21 (6.92–18.16), respectively, and the reporting rates were 9.62% and 5.54%, respectively. The RORs of bevacizumab, niraparib, and rucaparib were less than one.

RORs of leukemia and MDS in endometrial cancer

Carboplatin showed high RORs for both leukemia and MDS (Figures 6 and 7).

RORs of leukemia and MDS in other solid tumors

The RORs of leukemia and MDS in other solid tumors are shown in the supporting information (Supplimentary Figures S1–S14).

Reporting onset times of leukemia and MDS

The onset times of leukemia and MDS were extracted from the reports of patients with breast, colorectal, gastric, pancreatic, small cell lung, non-small cell lung, esophageal, ovarian, cervical, and endometrial

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Topoisomerase inhibitors				
Etoposide	3.68 (1.73-7.83)	28 / 1,671 (1.68%)	9 / 1,954 (0.46%)	***0.0003***
Irinotecan	1.10 (0.46-2.66)	6 / 541 (1.11%)	31 / 3,084 (1.01%)	0.8245
Topotecan	0.24 (0.03-1.74)	1 / 376 (0.27%)	36 / 3,249 (1.11%)	0.1241
Platinums				
Carboplatin	1.41 (0.72-2.74)	14 / 1,098 (1.28%)	23 / 2,527 (0.91%)	0.3152
Cisplatin	0.99 (0.49-2.00)	11 / 1,088 (1.01%)	26 / 2,537 (1.02%)	0.9698
Taxane				
Paclitaxel	*N/A*	0 / 145 (0.00%)	37 / 3,480 (1.06%)	0.2120
Molecular targeted drugs				
Immune checkpoint inhibitors				
Nivolumab	*N/A*	0 / 468 (0.00%)	37 / 3,157 (1.17%)	***0.0186***
Ipilimumab	*N/A*	0 / 358 (0.00%)	37 / 3,267 (1.13%)	***0.0430***

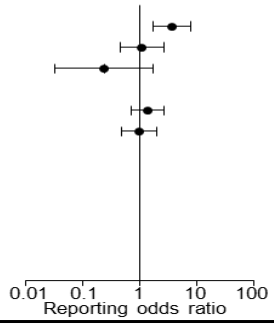

Figure 3. Reporting odds ratios of leukemia in small cell lung cancer.

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Carboplatin	3.31 (2.49-4.40)	114 / 5,745 (1.98%)	83 / 13,657 (0.61%)	***<0.0001***
Cisplatin	3.78 (2.47-5.78)	25 / 737 (3.39%)	172 / 18,665 (0.92%)	***<0.0001***
Oxaliplatin	1.28 (0.31-5.19)	2 / 155 (1.29%)	195 / 19,247 (1.01%)	0.7317
Taxanes				
Paclitaxel	3.49 (2.63-4.62)	106 / 4,916 (2.16%)	91 / 14,486 (0.63%)	***<0.0001***
Docetaxel	2.09 (1.10-3.98)	10 / 489 (2.04%)	187 / 18,913 (0.99%)	***0.0214***
Anthracycline				
Doxorubicin	4.94 (3.66-6.67)	66 / 1,843 (3.58%)	131 / 17,559 (0.75%)	***<0.0001***
Antimetabolites				
Gemcitabine	3.21 (2.22-4.65)	35 / 1,246 (2.81%)	162 / 18,156 (0.89%)	***<0.0001***
Capecitabine	0.83 (0.12-5.99)	1 / 118 (0.85%)	196 / 19,284 (1.02%)	0.8552
Topoisomerase inhibitors				
Topotecan	0.33 (0.08-1.34)	2 / 576 (0.35%)	195 / 18,826 (1.04%)	0.1044
Etoposide	11.17 (6.96-17.9)	21 / 224 (9.38%)	176 / 19,178 (0.92%)	***<0.0001***
Irinotecan	10.87 (5.58-21.2)	10 / 104 (9.62%)	187 / 19,298 (0.97%)	***<0.0001***
Alkylating agent				
Cyclophosphamide	11.40 (7.76-16.8)	34 / 379 (8.97%)	163 / 19,023 (0.86%)	***<0.0001***
Others				
Trabectedin	6.49 (3.56-11.8)	12 / 202 (5.94%)	185 / 19,200 (0.96%)	***<0.0001***
Thalidomide	*N/A*	0 / 125 (0.00%)	197 / 19,277 (1.02%)	0.2559
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	1.22 (0.87-1.70)	44 / 3,716 (1.18%)	153 / 15,686 (0.98%)	0.2539
PARP inhibitor				
Niraparib	0.45 (0.28-0.73)	18 / 3,525 (0.51%)	179 / 15,877 (1.13%)	***0.0010***
Rucaparib	0.42 (0.23-0.76)	12 / 2,575 (0.47%)	185 / 16,827 (1.10%)	***0.0028***
Olaparib	8.89 (6.63-11.9)	74 / 1,291 (5.73%)	123 / 18,111 (0.68%)	***<0.0001***
Immune checkpoint inhibitors				
Atezolizumab	*N/A*	0 / 182 (0.00%)	197 / 19,220 (1.02%)	0.1698
Nivolumab	*N/A*	0 / 159 (0.00%)	197 / 19,243 (1.02%)	0.1997
Pembrolizumab	*N/A*	0 / 129 (0.00%)	197 / 19,273 (1.02%)	0.2484
Multikinase inhibitor				
Pazopanib	*N/A*	0 / 168 (0.00%)	197 / 19,234 (1.02%)	0.1873
EGFR inhibitor				
Erlotinib	*N/A*	0 / 102 (0.00%)	197 / 19,300 (1.02%)	0.3051

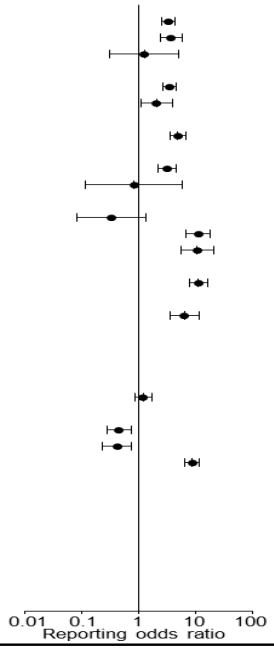

Figure 4. Reporting odds ratios of leukemia in ovarian cancer. VEGF: vascular endothelial growth factor, PARP: poly (ADP-ribose) polymerase, EGFR: epidermal growth factor receptor.

cancers. The reporting onset times of leukemia and MDS for each anticancer drug are shown in Figure 8. The median reporting onset times were 1.08–2.35 and 0.99–3.41 years for leukemia and MDS, respectively. Some cases of leukemia and MDS have been reported for over 20 years after chemotherapy. Approximately half of the cases of leukemia and MDS have been reported 1–4 years after chemotherapy. The results of the anticancer drugs that significantly increased the risk of leukemia and MDS are shown in Figures 2–7. Reports without information regarding the onset time were excluded.

DISCUSSION

Leukemia and MDS accounted for 0.07–1.06% and 0.08–0.83% of adverse event reports in FAERS, respectively, for each solid cancer in our study. These reporting rates do not refer to the incidence rates after the use of an anticancer drug because they were calculated in this study by dividing the number of leukemia and MDS reports by the total number of adverse event reports. However, these results demonstrate that a considerable number of patients develop secondary leukemia and MDS.

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Carboplatin	1.65 (1.14-2.37)	49 / 5,745 (0.85%)	71 / 13,657 (0.52%)	***0.0069***
Cisplatin	3.39 (1.93-5.95)	14 / 737 (1.90%)	106 / 18,665 (0.57%)	***<0.0001***
Oxaliplatin	2.12 (0.52-8.65)	2 / 155 (1.29%)	118 / 19,247 (0.61%)	0.2841
Taxanes				
Paclitaxel	1.84 (1.27-2.66)	46 / 4,916 (0.94%)	74 / 14,486 (0.51%)	***0.0010***
Docetaxel	3.57 (1.86-6.86)	10 / 489 (2.04%)	110 / 18,913 (0.58%)	***<0.0001***
Anthracycline				
Doxorubicin	2.15 (1.35-3.43)	22 / 1,843 (1.19%)	98 / 17,559 (0.56%)	***0.0009***
Antimetabolites				
Gemcitabine	1.33 (0.69-2.54)	10 / 1,246 (0.80%)	110 / 18,156 (0.61%)	0.3916
Capecitabine	2.80 (0.68-11.5)	2 / 118 (1.69%)	118 / 19,284 (0.61%)	0.1347
Topoisomerase inhibitors				
Topotecan	1.42 (0.58-3.50)	5 / 576 (0.87%)	115 / 18,826 (0.61%)	0.4380
Etoposide	3.78 (1.53-9.36)	5 / 224 (2.23%)	115 / 19,178 (0.60%)	***0.0019***
Irinotecan	18.56 (9.42-36.6)	10 / 104 (9.62%)	110 / 19,298 (0.57%)	***<0.0001***
Alkylating agent				
Cyclophosphamide	11.21 (6.92-18.2)	21 / 379 (5.54%)	99 / 19,023 (0.52%)	***<0.0001***
Others				
Trabectedin	*N/A*	0 / 202 (0.00%)	120 / 19,200 (0.63%)	0.2597
Thalidomide	1.30 (0.18-9.37)	1 / 125 (0.80%)	119 / 19,277 (0.62%)	0.7951
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	0.34 (0.17-0.67)	9 / 3,716 (0.24%)	111 / 15,686 (0.71%)	***0.0011***
PARP inhibitor				
Niraparib	0.45 (0.24-0.84)	11 / 3,525 (0.31%)	109 / 15,877 (0.69%)	***0.0103***
Rucaparib	0.22 (0.08-0.61)	4 / 2,575 (0.16%)	116 / 16,827 (0.69%)	***0.0013***
Olaparib	9.67 (6.68-14.0)	48 / 1,291 (3.72%)	72 / 18,111 (0.40%)	***<0.0001***
Immune checkpoint inhibitors				
Atezolizumab	0.89 (0.12-6.38)	1 / 182 (0.55%)	119 / 19,220 (0.62%)	0.9050
Nivolumab	1.02 (0.14-7.33)	1 / 159 (0.63%)	119 / 19,243 (0.62%)	0.9866
Pembrolizumab	*N/A*	0 / 129 (0.00%)	120 / 19,273 (0.62%)	0.3687
Multikinase inhibitor				
Pazopanib	*N/A*	0 / 168 (0.00%)	120 / 19,234 (0.62%)	0.3044
EGFR inhibitor				
Erlotinib	*N/A*	0 / 102 (0.00%)	120 / 19,300 (0.62%)	0.4244

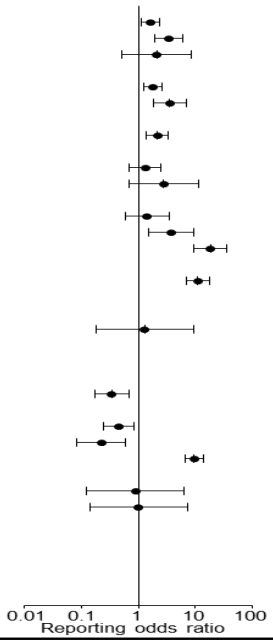

Figure 5. Reporting odds ratios of myelodysplastic syndrome (MDS) in ovarian cancer. VEGF: vascular endothelial growth factor, PARP: poly (ADP-ribose) polymerase, EGFR: epidermal growth factor receptor.

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Taxane				
Paclitaxel	4.38 (1.37-14.1)	10 / 484 (2.07%)	4 / 835 (0.48%)	***0.0067***
Platinums				
Carboplatin	25.12 (3.28-192.8)	13 / 458 (2.84%)	1 / 861 (0.12%)	***<0.0001***
Cisplatin	2.53 (0.79-8.16)	4 / 182 (2.20%)	10 / 1,137 (0.88%)	0.1071
Anthracycline				
Doxorubicin	0.42 (0.05-3.19)	1 / 205 (0.49%)	13 / 1,114 (1.17%)	0.3832
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 209 (0.00%)	14 / 1,110 (1.26%)	0.1026

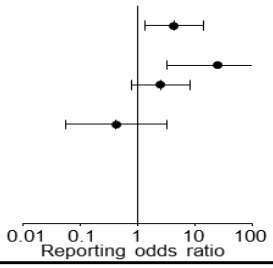

Figure 6. Reporting odds ratios of leukemia in endometrial cancer. VEGF: vascular endothelial growth factor.

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Taxane				
Paclitaxel	3.05 (0.89-10.5)	7 / 484 (1.45%)	4 / 835 (0.48%)	0.0626
Platinums				
Carboplatin	19.20 (2.45-150.4)	10 / 458 (2.18%)	1 / 861 (0.12%)	***<0.0001***
Cisplatin	*N/A*	0 / 182 (0.00%)	11 / 1,137 (0.97%)	0.1827
Anthracycline				
Doxorubicin	*N/A*	0 / 205 (0.00%)	11 / 1,114 (0.99%)	0.1531
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 209 (0.00%)	11 / 1,110 (0.99%)	0.1484

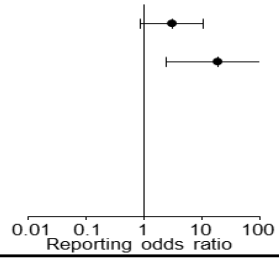

Figure 7. Reporting odds ratios of myelodysplastic syndrome (MDS) in endometrial cancer. VEGF: vascular endothelial growth factor.

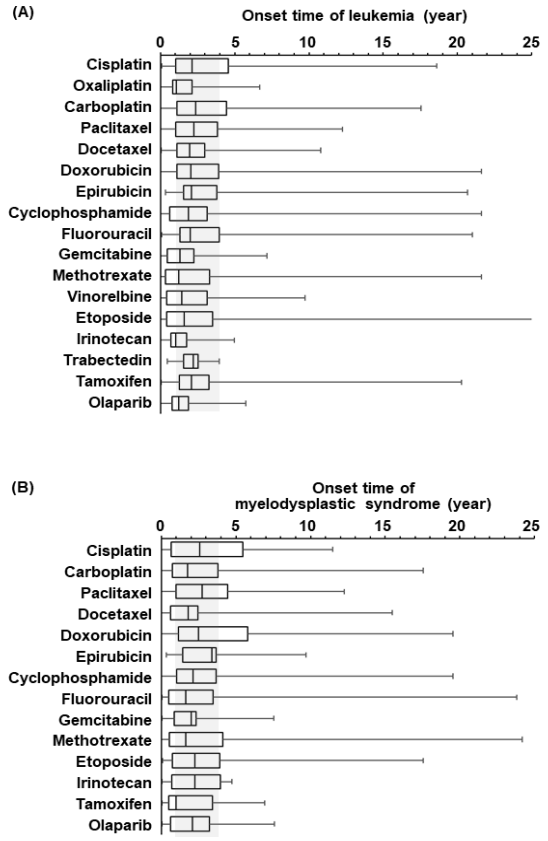

Figure 8. Reporting onset times of leukemia (A) and myelodysplastic syndrome (MDS) (B).

When analyzed by cancer type, the reporting rates of leukemia were high in breast, small cell lung, ovarian, and endometrial cancers, and low in colorectal, pancreatic, and non-small cell lung cancers. One factor that affects the difference in reporting rates among cancer types is the difference in life expectancy for each cancer. For example, leukemia was more likely to be reported in breast cancer patients because breast cancer has a good prognosis, and the opposite is true for pancreatic cancer. Another factor that affects reporting rates is the difference in the type of anticancer drug used.

Many previous reports have indicated secondary malignancies in breast cancer patients (9–12). In our study, patients receiving cytocidal anticancer drugs, including taxanes (paclitaxel and docetaxel), anthracyclines (doxorubicin and epirubicin), alkylating agents (cyclophosphamide), and antimetabolites (fluorouracil and methotrexate), had significantly higher reported rates of leukemia in the reports of breast cancer. These drugs are widely used as adjuvant chemotherapy for breast cancer (13–15). Thus, medical oncologists, clinical pharmacists, and patients should fully understand and consider the risks of secondary leukemia when initiating adjuvant therapy for breast cancer. Taxanes, anthracyclines, alkylating agents, and antimetabolites showed high RORs for leukemia in cancer types other than breast cancer. Several genetic abnormalities have been reported in patients with therapy-related AML and MDS (16). AML after chemotherapy with anthracyclines, which are DNA-topoisomerase II inhibitors, is often associated with chromosomal translocations involving chromosome bands 11q23 (*MLL*) and 21q22 (*RUNX1*) (17,18). Monosomy 5/deletion 5q, monosomy 7/deletion 7q, or both, are found in patients with AML after alkylating agents (18). These effects on the chromosome are considered to be the major mechanisms of t-MN induced by cytocidal anticancer drugs. In addition, patients on molecular targeted agents, including HER inhibitors (trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine, and neratinib), cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib), and vascular endothelial growth factor (VEGF) inhibitors (bevacizumab), had significantly lower reported rates of leukemia in the reports of breast cancer in this study. These results may be because molecular targeted drugs are less likely to cause chromosomal abnormalities than cytotoxic anticancer drugs. Another reason could be that CDK4/6 inhibitors, VEGF inhibitors, and trastuzumab emtansine are often used for advanced breast cancer (19–21) rather than adjuvant chemotherapy. Regardless, it can be concluded that t-MN after molecular-targeted chemotherapy is less of a problem in breast cancer patients. Regarding hormonal agents, only tamoxifen was associated with a high risk of leukemia. Tamoxifen was previously reported to be a risk factor for endometrial cancer (22). Several mechanisms, such as estrogenic effects, the mammalian target of the rapamycin (mTOR) autophagy signaling pathway, DNA damage, and effects on driver genes, are involved in the induction of endometrial cancer by tamoxifen (23). Some of these mechanisms may also be involved in the development of t-MN. Because many patients take tamoxifen, patients and medical teams need to be aware of the risks of t-MN.

Among cancer types other than breast cancer, there was a tendency for cytocidal drugs to increase the risk of leukemia, whereas molecular targeted drugs had a low risk. Platinum showed high RORs in colorectal (Supplementary Figure S2), gastric (Supplementary Figure S4), non-small cell lung (Supplementary Figure S9), ovarian, cervical (Supplementary Figure S13), and endometrial

cancers, and topoisomerase inhibitors showed high RORs in small cell lung, non-small cell lung (Supplementary Figure S9), and ovarian cancers. Previous studies have reported that the use of cisplatin, a platinum drug, approximately triples the risk of leukemia in ovarian and testicular cancer (24, 25). Cytocidal anticancer drugs could be considered a risk factor for t-MN in almost all types of cancer. In addition, there have been few reports of leukemia in patients treated with immune checkpoint inhibitors. Considering the mechanism of action, the risk of t-MN due to immune checkpoint inhibitors is considered low. However, since the use of immune checkpoint inhibitors has recently increased, it is necessary to continue collecting information. In this study, we analyzed both leukemia and MDS, and found a correlation between the risk of leukemia and MDS for each drug and cancer type.

Approximately half of the cases of leukemia and MDS were reported 1–4 years after chemotherapy in our analysis. Some cases of leukemia and MDS have been reported for over 20 years after chemotherapy. A previous report also indicated the risk of secondary cancer up to 40 years after treatment in patients with Hodgkin's lymphoma (26). Since t-MN is a long-term adverse event, it must be considered when initiating chemotherapy in children, adolescents, young adults, and other young people.

Since t-MN occurs less frequently than other adverse effects associated with chemotherapy, including nausea, vomiting, and bone marrow suppression, it is easily neglected when chemotherapy is initiated. Other adverse effects, such as nausea, vomiting, and neutropenia, can be treated with supportive care; however, it can often be fatal or challenging. Thus, medical oncologists, clinical pharmacists, and patients should consider the t-MN risk of each drug in each cancer type when selecting chemotherapy regimens. There have been many studies on t-MN since early times (9-12,22,24,25,27-32). Most of these studies were limited to cancer types and causative agents, and had a small number of cases (9-12,22,24,25,27-30). Recently, large-scale studies on secondary cancers have been reported (33-37). Chaturvedi AK. and colleagues studied the risk of second cancers in cervical cancer with radiation treatment, using data from 104,760 one-year survivors of cervical cancer reported to 13 population-based cancer registries in Denmark, Finland, Norway, Sweden, and the United States (33). They reported that cervical cancer patients treated with radiotherapy are at an increased risk of second cancers beyond 40 years of follow-up (33). Moreover, Ju HY. and colleagues reported that childhood cancer survivors were at a 20-fold higher risk of developing a malignant neoplasm compared to the general population, through a registry-based study of 5.6 years of follow-up using the medical data from the Korea Central Cancer Registry (28,405 patients) (36). Furthermore, a study by Morton LM. and colleagues assessed the tMDS/AML risk after chemotherapy for solid cancer using cancer registries from the Surveillance, Epidemiology, and End Results Program and Medicare claims (700,612 patients) (37). These large studies take a great deal of time and effort and therefore have a large number of cases and reliable data. However, these studies are limited in terms of cancer type and other conditions, and there is a lack of data assessing which drugs are associated with a higher risk. Our study assessed the risk of t-MN with each drug in each cancer type, which has not been assessed in previous studies. Although there are some problems with adverse event reporting databases, such as data heterogeneity, they are useful tools for analyzing large-scale and comprehensive information. Our data may not directly reflect the risks associated with the drugs themselves. However, these data seem to reflect cases that are based on actual reports (i.e., cases that may present problems in clinical practice). The results of our analysis using a large adverse event database may compensate for the lack of previous studies on the t-MN risk of each drug in each cancer.

CONCLUSION

This study clarified the risks of t-MN for several anticancer drugs in patients with different solid tumors. The data presented here and in the supporting information (Supplementary Figures S1-S14) could be useful for assessing the risks of secondary leukemia and MDS when medical oncologists, clinical pharmacists, and patients select chemotherapy regimens.

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CONFLICT OF INTEREST STATEMENT. The authors declare no conflicts of interest associated with this manuscript.

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Analysis of Secondary Leukemia and Myelodysplastic Syndrome After Chemotherapy for Solid Organ Tumors Using the Food and Drug Administration Adverse Event Reporting System (FAERS)

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SUPPLEMENTS

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Antimetabolites				
Fluorouracil	2.74 (0.65-11.5)	5 / 4,353 (0.11%)	3 / 7,146 (0.04%)	0.1505
Capecitabine	0.45 (0.05-3.64)	1 / 2,783 (0.04%)	7 / 8,716 (0.08%)	0.4395
Tipiracil; trifluridine	*N/A*	0 / 136 (0.00%)	8 / 11,363 (0.07%)	0.7569
Platinum				
Oxaliplatin	14.18 (1.74-115.3)	7 / 3,805 (0.18%)	1 / 7,694 (0.01%)	***0.0011***
Topoisomerase inhibitor				
Irinotecan	1.73 (0.41-7.25)	3 / 2,960 (0.10%)	5 / 8,539 (0.06%)	0.4467
Molecular targeted drugs				
VEGF inhibitors				
Bevacizumab	*N/A*	0 / 3,667 (0.00%)	8 / 7,832 (0.10%)	0.0529
Aflibercept	*N/A*	0 / 127 (0.00%)	8 / 11,372 (0.07%)	0.7649
EGFR inhibitors				
Panitumumab	*N/A*	0 / 1,763 (0.00%)	8 / 9,736 (0.08%)	0.2286
Cetuximab	1.00 (0.12-8.13)	1 / 1,438 (0.07%)	7 / 10,061 (0.07%)	0.9996
Multikinase inhibitor				
Regorafenib	*N/A*	0 / 769 (0.00%)	8 / 10,730 (0.07%)	0.4488
MEK inhibitor				
Trametinib	*N/A*	0 / 132 (0.00%)	8 / 11,367 (0.07%)	0.7604
B-RAF inhibitor				
Dabrafenib	*N/A*	0 / 104 (0.00%)	8 / 11,395 (0.07%)	0.7869

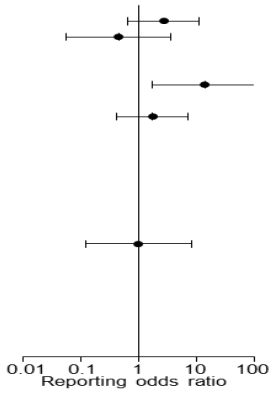

Figure S2. Reporting odds ratios of leukemia in colorectal cancer. VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Antimetabolites				
Fluorouracil	0.27 (0.03-2.27)	1 / 4,353 (0.02%)	6 / 7,146 (0.08%)	0.1984
Capecitabine	1.25 (0.24-6.46)	2 / 2,783 (0.07%)	5 / 8,716 (0.06%)	0.7872
Tipiracil; trifluridine	*N/A*	0 / 136 (0.00%)	7 / 11,363 (0.06%)	0.7722
Platinum				
Oxaliplatin	2.70 (0.60-12.1)	4 / 3,805 (0.11%)	3 / 7,694 (0.04%)	0.1761
Topoisomerase inhibitor				
Irinotecan	*N/A*	0 / 2,960 (0.00%)	7 / 8,539 (0.08%)	0.1192
Molecular targeted drugs				
VEGF inhibitors				
Bevacizumab	*N/A*	0 / 3,667 (0.00%)	7 / 7,832 (0.09%)	0.0702
Aflibercept	*N/A*	0 / 127 (0.00%)	7 / 11,372 (0.06%)	0.7797
EGFR inhibitors				
Panitumumab	*N/A*	0 / 1,763 (0.00%)	7 / 9,736 (0.07%)	0.2601
Cetuximab	*N/A*	0 / 1,438 (0.00%)	7 / 10,061 (0.07%)	0.3170
Multikinase inhibitor				
Regorafenib	*N/A*	0 / 769 (0.00%)	7 / 10,730 (0.07%)	0.4786
MEK inhibitor				
Trametinib	*N/A*	0 / 132 (0.00%)	7 / 11,367 (0.06%)	0.7755
B-RAF inhibitor				
Dabrafenib	*N/A*	0 / 104 (0.00%)	7 / 11,395 (0.06%)	0.8004

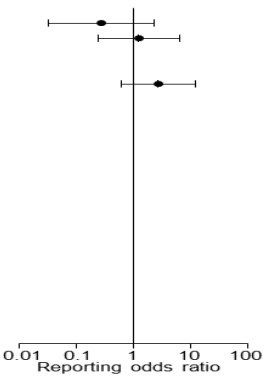

Figure S3. Reporting odds ratios of myelodysplastic syndromes in colorectal cancer. VEGF, vascular endothelial growth f actor; EGFR, epidermal growth factor receptor; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	p value
Cytotoxic agents				
Antimetabolites				
Capecitabine	0.83 (0.29-2.36)	5 / 2,295 (0.22%)	12 / 4,571 (0.26%)	0.7254
Fluorouracil	1.57 (0.51-4.83)	4 / 1,125 (0.36%)	13 / 5,741 (0.23%)	0.4256
Gimeracil;oteracil;tegafur	2.42 (0.55-10.6)	2 / 360 (0.56%)	15 / 6,506 (0.23%)	0.2271
Platinums				
Cisplatin	0.60 (0.17-2.10)	3 / 1,799 (0.17%)	14 / 5,067 (0.28%)	0.4219
Oxaliplatin	3.38 (1.28-8.89)	7 / 1,183 (0.59%)	10 / 5,683 (0.18%)	***0.0089***
Taxanes				
Paclitaxel	0.38 (0.05-2.89)	1 / 963 (0.10%)	16 / 5,903 (0.27%)	0.3330
Docetaxel	0.65 (0.09-4.88)	1 / 605 (0.17%)	16 / 6,261 (0.26%)	0.6697
Anthracyclines				
Epirubicin	*N/A*	0 / 797 (0.00%)	17 / 6,069 (0.28%)	0.1347
Topoisomerase inhibitor				
Irinotecan	2.82 (0.81-9.86)	3 / 486 (0.62%)	14 / 6,380 (0.22%)	0.0889
Molecular targeted drugs				
VEGF inhibitors				
Ramucirumab	*N/A*	0 / 643 (0.00%)	17 / 6,223 (0.27%)	0.1845
Bevacizumab	*N/A*	0 / 535 (0.00%)	17 / 6,331 (0.27%)	0.2301
HER inhibitors				
Trastuzumab	0.73 (0.10-5.48)	1 / 544 (0.18%)	16 / 6,322 (0.25%)	0.7551
Immune checkpoint inhibitors				
Nivolumab	*N/A*	0 / 449 (0.00%)	17 / 6,417 (0.26%)	0.2748
Tyrosine kinase inhibitors				
Imatinib	4.66 (1.33-16.3)	3 / 304 (0.99%)	14 / 6,562 (0.21%)	***0.0080***
Sunitinib	*N/A*	0 / 106 (0.00%)	17 / 6,760 (0.25%)	0.6052

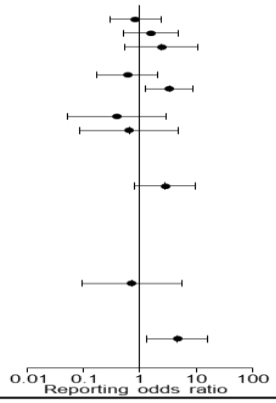

Figure S4. Reporting odds ratios for leukemia in gastric cancer. VEGF: vascular endothelial growth factor; HER: human epidermal growth factor receptor

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	p value
Cytotoxic agents				
Antimetabolites				
Capecitabine	0.33 (0.04-2.76)	1 / 2,295 (0.04%)	6 / 4,571 (0.13%)	0.2828
Fluorouracil	2.04 (0.40-10.5)	2 / 1,125 (0.18%)	5 / 5,741 (0.09%)	0.3835
Gimeracil;oteracil;tegafur	13.66 (3.05-61.3)	3 / 360 (0.83%)	4 / 6,506 (0.06%)	***<0.0001***
Platinums				
Cisplatin	2.11 (0.47-9.46)	3 / 1,799 (0.17%)	4 / 5,067 (0.08%)	0.3160
Oxaliplatin	*N/A*	0 / 1,183 (0.00%)	7 / 5,683 (0.12%)	0.2271
Taxanes				
Paclitaxel	8.20 (1.83-36.7)	4 / 963 (0.42%)	3 / 5,903 (0.05%)	***0.0010***
Docetaxel	1.73 (0.21-14.4)	1 / 605 (0.17%)	6 / 6,261 (0.10%)	0.6092
Anthracyclines				
Epirubicin	*N/A*	0 / 797 (0.00%)	7 / 6,069 (0.12%)	0.3374
Topoisomerase inhibitor				
Irinotecan	2.19 (0.26-18.2)	1 / 486 (0.21%)	6 / 6,380 (0.09%)	0.4569
Molecular targeted drugs				
VEGF inhibitors				
Ramucirumab	1.61 (0.19-13.4)	1 / 643 (0.16%)	6 / 6,223 (0.10%)	0.6548
Bevacizumab	*N/A*	0 / 535 (0.00%)	7 / 6,331 (0.11%)	0.4416
HER inhibitors				
Trastuzumab	4.66 (0.90-24.1)	2 / 544 (0.37%)	5 / 6,322 (0.08%)	***0.0430***
Immune checkpoint inhibitors				
Nivolumab	*N/A*	0 / 449 (0.00%)	7 / 6,417 (0.11%)	0.4838
Tyrosine kinase inhibitors				
Imatinib	*N/A*	0 / 304 (0.00%)	7 / 6,562 (0.11%)	0.5688
Sunitinib	*N/A*	0 / 106 (0.00%)	7 / 6,760 (0.10%)	0.7403

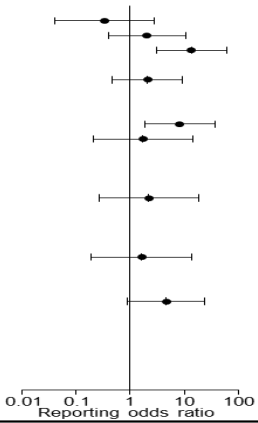

Figure S5. Reporting odds ratios for myelodysplastic syndrome in gastric cancer. VEGF: vascular endothelial growth factor; HER: human epidermal growth factor receptor

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	p value
Cytotoxic agents				
Antimetabolites				
Gemcitabine	4.59 (1.28-16.5)	11 / 5,498 (0.20%)	3 / 6,870 (0.04%)	***0.0102***
Capecitabine	0.63 (0.08-4.85)	1 / 1,337 (0.07%)	13 / 11,031 (0.12%)	0.6584
Fluorouracil	*N/A*	0 / 1,305 (0.00%)	14 / 11,063 (0.13%)	0.1985
Gimeracil;oteracil;tegafur	*N/A*	0 / 105 (0.00%)	14 / 12,263 (0.11%)	0.7290
Taxanes				
Paclitaxel	*N/A*	0 / 1,959 (0.00%)	14 / 10,409 (0.13%)	0.1043
Docetaxel	*N/A*	0 / 235 (0.00%)	14 / 12,133 (0.12%)	0.6023
Platinums				
Oxaliplatin	*N/A*	0 / 1,427 (0.00%)	14 / 10,941 (0.13%)	0.1764
Cisplatin	*N/A*	0 / 315 (0.00%)	14 / 12,053 (0.12%)	0.5450
Topoisomerase inhibitor				
Irinotecan	*N/A*	0 / 1,098 (0.00%)	14 / 11,270 (0.12%)	0.2426
Other				
Thalidomide	*N/A*	0 / 108 (0.00%)	14 / 12,260 (0.11%)	0.7253
Molecular targeted drugs				
EGFR inhibitors				
Erlotinib	1.21 (0.38-3.85)	4 / 3,080 (0.13%)	10 / 9,288 (0.11%)	0.7508
Cetuximab	*N/A*	0 / 240 (0.00%)	14 / 12,128 (0.12%)	0.5984
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 592 (0.00%)	14 / 11,776 (0.12%)	0.4012
Multikinase inhibitor				
Sunitinib	*N/A*	0 / 198 (0.00%)	14 / 12,170 (0.12%)	0.6330
Immune checkpoint inhibitor				
Nivolumab	*N/A*	0 / 184 (0.00%)	14 / 12,184 (0.11%)	0.6455
mTOR inhibitor				
Everolimus	*N/A*	0 / 163 (0.00%)	14 / 12,205 (0.11%)	0.6653

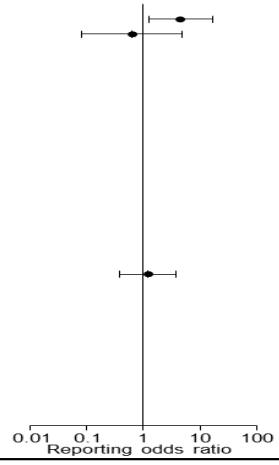

Figure S6. Reporting odds ratios for leukemia in pancreatic cancer. VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Antimetabolites				
Gemcitabine	0.83 (0.23-2.95)	4 / 5,498 (0.07%)	6 / 6,870 (0.09%)	0.7768
Capecitabine	*N/A*	0 / 1,337 (0.00%)	10 / 11,031 (0.09%)	0.2702
Fluorouracil	2.12 (0.45-10.0)	2 / 1,305 (0.15%)	8 / 11,063 (0.07%)	0.3306
Gimeracil;oteracil;tegafur	*N/A*	0 / 105 (0.00%)	10 / 12,263 (0.08%)	0.7697
Taxanes				
Paclitaxel	1.33 (0.28-6.26)	2 / 1,959 (0.10%)	8 / 10,409 (0.08%)	0.7185
Docetaxel	*N/A*	0 / 235 (0.00%)	10 / 12,133 (0.08%)	0.6597
Platinums				
Oxaliplatin	1.92 (0.41-9.04)	2 / 1,427 (0.14%)	8 / 10,941 (0.07%)	0.4021
Cisplatin	16.55 (4.26-64.3)	3 / 315 (0.95%)	7 / 12,053 (0.06%)	***<0.0001***
Topoisomerase inhibitor				
Irinotecan	6.86 (1.93-24.4)	4 / 1,098 (0.36%)	6 / 11,270 (0.05%)	***0.0005***
Other				
Thalidomide	*N/A*	0 / 108 (0.00%)	10 / 12,260 (0.08%)	0.7665
Molecular targeted drugs				
EGFR inhibitors				
Erlotinib	0.33 (0.04-2.64)	1 / 3,080 (0.03%)	9 / 9,288 (0.10%)	0.2756
Cetuximab	*N/A*	0 / 240 (0.00%)	10 / 12,128 (0.08%)	0.6563
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 592 (0.00%)	10 / 11,776 (0.08%)	0.4781
Multikinase inhibitor				
Sunitinib	*N/A*	0 / 198 (0.00%)	10 / 12,170 (0.08%)	0.6866
Immune checkpoint inhibitor				
Nivolumab	*N/A*	0 / 184 (0.00%)	10 / 12,184 (0.08%)	0.6974
mTOR inhibitor				
Everolimus	*N/A*	0 / 163 (0.00%)	10 / 12,205 (0.08%)	0.7147

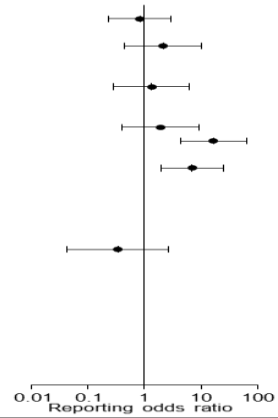

Figure S7. Reporting odds ratios for myelodysplastic syndrome in pancreatic cancer. VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Topoisomerase inhibitors				
Etoposide	5.29 (1.14-24.5)	9 / 1,671 (0.54%)	2 / 1,954 (0.10%)	***0.0173***
Irinotecan	2.14 (0.57-8.11)	3 / 541 (0.55%)	8 / 3,084 (0.26%)	0.2497
Topotecan	*N/A*	0 / 376 (0.00%)	11 / 3,249 (0.34%)	0.2585
Platinums				
Carboplatin	6.17 (1.64-23.3)	8 / 1,098 (0.73%)	3 / 2,527 (0.12%)	***0.0022***
Cisplatin	10.57 (2.28-49.0)	9 / 1,088 (0.83%)	2 / 2,537 (0.08%)	***0.0002***
Taxane				
Paclitaxel	30.00 (9.05-99.5)	6 / 145 (4.14%)	5 / 3,480 (0.14%)	***<0.0001***
Molecular targeted drugs				
Immune checkpoint inhibitor				
Nivolumab	*N/A*	0 / 468 (0.00%)	11 / 3,157 (0.35%)	0.2009
Ipilimumab	*N/A*	0 / 358 (0.00%)	11 / 3,267 (0.34%)	0.2715

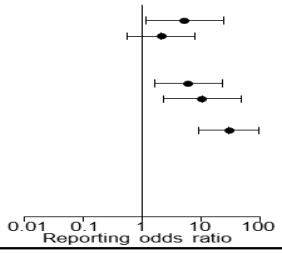

Figure S8. Reporting odds ratios for myelodysplastic syndrome in small cell lung cancer

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Carboplatin	2.97 (1.63-5.42)	18 / 6,992 (0.26%)	26 / 29,938 (0.09%)	***0.0002***
Cisplatin	7.79 (4.30-14.1)	20 / 3,583 (0.56%)	24 / 33,347 (0.07%)	***<0.0001***
Antimetabolites				
Pemetrexed	0.72 (0.26-2.03)	4 / 4,478 (0.09%)	40 / 32,452 (0.12%)	0.5372
Gemcitabine	3.69 (1.86-7.31)	11 / 3,068 (0.36%)	33 / 33,862 (0.10%)	***<0.0001***
Taxanes				
Paclitaxel	3.22 (1.68-6.15)	13 / 4,269 (0.30%)	31 / 32,661 (0.09%)	***0.0002***
Docetaxel	7.05 (3.73-13.3)	14 / 2,305 (0.61%)	30 / 34,625 (0.09%)	***<0.0001***
Vinca alkaloid				
Vinorelbine	5.13 (2.28-11.5)	7 / 1,320 (0.53%)	37 / 35,610 (0.10%)	***<0.0001***
Topoisomerase inhibitors				
Etoposide	28.84 (13.8-60.5)	9 / 335 (2.69%)	35 / 36,595 (0.10%)	***<0.0001***
Irinotecan	8.12 (1.95-33.8)	2 / 217 (0.92%)	42 / 36,713 (0.11%)	***0.0006***
Other				
Thalidomide	*N/A*	0 / 138 (0.00%)	44 / 36,792 (0.12%)	0.6844
Molecular targeted drugs				
EGFR inhibitors				
Erlotinib	0.69 (0.29-1.64)	6 / 6,835 (0.09%)	38 / 30,095 (0.13%)	0.4051
Gefitinib	2.22 (0.88-5.65)	5 / 2,015 (0.25%)	39 / 34,915 (0.11%)	0.0843
Afatinib	0.55 (0.08-3.99)	1 / 1,501 (0.07%)	43 / 35,429 (0.12%)	0.5470
Osimertinib	1.18 (0.29-4.89)	2 / 1,430 (0.14%)	42 / 35,500 (0.12%)	0.8168
Cetuximab	0.62 (0.08-4.48)	1 / 1,341 (0.07%)	43 / 35,589 (0.12%)	0.6298
Necitumumab	*N/A*	0 / 151 (0.00%)	44 / 36,779 (0.12%)	0.6706
Immune checkpoint inhibitors				
Nivolumab	0.13 (0.02-0.97)	1 / 5,463 (0.02%)	43 / 31,467 (0.14%)	0.0913
Pembrolizumab	*N/A*	0 / 1,759 (0.00%)	44 / 35,171 (0.13%)	0.1377
Ipilimumab	*N/A*	0 / 675 (0.00%)	44 / 36,255 (0.12%)	0.3651
Atezolizumab	*N/A*	0 / 660 (0.00%)	44 / 36,270 (0.12%)	0.3706
Durvalumab	1.64 (0.23-11.9)	1 / 517 (0.19%)	43 / 36,413 (0.12%)	0.6220
VEGF inhibitors				
Bevacizumab	0.20 (0.03-1.47)	1 / 3,798 (0.03%)	43 / 33,132 (0.13%)	0.0800
Ramucirumab	*N/A*	0 / 222 (0.00%)	44 / 36,708 (0.12%)	0.6057
ALK inhibitors				
Crizotinib	0.50 (0.07-3.62)	1 / 1,646 (0.06%)	43 / 35,284 (0.12%)	0.4823
Ceritinib	*N/A*	0 / 598 (0.00%)	44 / 36,332 (0.12%)	0.3945
Alectinib	*N/A*	0 / 314 (0.00%)	44 / 36,616 (0.12%)	0.5388
Triple angiokinase inhibitor				
Nintedanib	*N/A*	0 / 293 (0.00%)	44 / 36,637 (0.12%)	0.5528
Multikinase inhibitors				
Sorafenib	*N/A*	0 / 201 (0.00%)	44 / 36,729 (0.12%)	0.6234
Sunitinib	*N/A*	0 / 167 (0.00%)	44 / 36,763 (0.12%)	0.6546
B-RAF inhibitor				
Dabrafenib	*N/A*	0 / 170 (0.00%)	44 / 36,760 (0.12%)	0.6517
MEK inhibitor				
Trametinib	*N/A*	0 / 170 (0.00%)	44 / 36,760 (0.12%)	0.6517
Proteasome inhibitor				
Bortezomib	*N/A*	0 / 126 (0.00%)	44 / 36,804 (0.12%)	0.6978

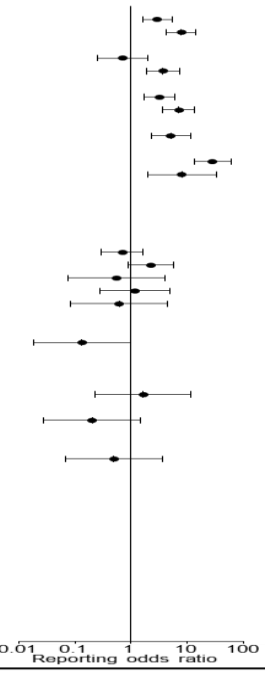

Figure S9. Reporting odds ratios for leukemia in non-small cell lung cancer. VEGF, vascular endothelial growth factor; ALK, anaplastic lymphoma kinase; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Carboplatin	5.25 (2.81-9.79)	22 / 6,992 (0.31%)	18 / 29,938 (0.06%)	***<0.0001***
Cisplatin	2.33 (1.07-5.06)	8 / 3,583 (0.22%)	32 / 33,347 (0.10%)	***0.0277***
Antimetabolites				
Pemetrexed	0.81 (0.29-2.26)	4 / 4,478 (0.09%)	36 / 32,452 (0.11%)	0.6803
Gemcitabine	1.95 (0.82-4.65)	6 / 3,068 (0.20%)	34 / 33,862 (0.10%)	0.1249
Taxanes				
Paclitaxel	3.69 (1.90-7.16)	13 / 4,269 (0.30%)	27 / 32,661 (0.08%)	***<0.0001***
Docetaxel	1.22 (0.38-3.95)	3 / 2,305 (0.13%)	37 / 34,625 (0.11%)	0.7420
Vinca alkaloid				
Vinorelbine	4.78 (2.00-11.4)	6 / 1,320 (0.45%)	34 / 35,610 (0.10%)	***<0.0001***
Topoisomerase inhibitors				
Etoposide	23.65 (10.4-53.8)	7 / 335 (2.09%)	33 / 36,595 (0.09%)	***<0.0001***
Irinotecan	4.35 (0.60-31.8)	1 / 217 (0.46%)	39 / 36,713 (0.11%)	0.1133
Other				
Thalidomide	*N/A*	0 / 138 (0.00%)	40 / 36,792 (0.11%)	0.6983
Molecular targeted drugs				
EGFR inhibitors				
Erlotinib	0.36 (0.11-1.16)	3 / 6,835 (0.04%)	37 / 30,095 (0.12%)	0.0729
Gefitinib	0.91 (0.22-3.78)	2 / 2,015 (0.10%)	38 / 34,915 (0.11%)	0.8988
Afatinib	*N/A*	0 / 1,501 (0.00%)	40 / 35,429 (0.11%)	0.1927
Osimertinib	0.64 (0.09-4.63)	1 / 1,430 (0.07%)	39 / 35,500 (0.11%)	0.2030
Cetuximab	*N/A*	0 / 1,341 (0.00%)	40 / 35,589 (0.11%)	0.2193
Necitumumab	*N/A*	0 / 151 (0.00%)	40 / 36,779 (0.11%)	0.6851
Immune checkpoint inhibitors				
Nivolumab	0.82 (0.32-2.10)	5 / 5,463 (0.09%)	35 / 31,467 (0.11%)	0.6828
Pembrolizumab	2.22 (0.79-6.26)	4 / 1,759 (0.23%)	36 / 35,171 (0.10%)	0.1197
Ipilimumab	*N/A*	0 / 675 (0.00%)	40 / 36,255 (0.11%)	0.3879
Atezolizumab	1.41 (0.19-10.3)	1 / 660 (0.15%)	39 / 36,270 (0.11%)	0.7335
Durvalumab	*N/A*	0 / 517 (0.00%)	40 / 36,413 (0.11%)	0.4508
VEGF inhibitors				
Bevacizumab	0.46 (0.11-1.90)	2 / 3,798 (0.05%)	38 / 33,132 (0.11%)	0.2710
Ramucirumab	*N/A*	0 / 222 (0.00%)	40 / 36,708 (0.11%)	0.6226
ALK inhibitors				
Crizotinib	*N/A*	0 / 1,646 (0.00%)	40 / 35,284 (0.11%)	0.1717
Ceritinib	*N/A*	0 / 598 (0.00%)	40 / 36,332 (0.11%)	0.4169
Alectinib	*N/A*	0 / 314 (0.00%)	40 / 36,616 (0.11%)	0.5579
Triple angiokinase inhibitor				
Nintedanib	*N/A*	0 / 293 (0.00%)	40 / 36,637 (0.11%)	0.5715
Multikinase inhibitors				
Sorafenib	*N/A*	0 / 201 (0.00%)	40 / 36,729 (0.11%)	0.6397
Sunitinib	*N/A*	0 / 167 (0.00%)	40 / 36,763 (0.11%)	0.6697
B-RAF inhibitor				
Dabrafenib	*N/A*	0 / 170 (0.00%)	40 / 36,760 (0.11%)	0.6670
MEK inhibitor				
Trametinib	*N/A*	0 / 170 (0.00%)	40 / 36,760 (0.11%)	0.6670
Proteasome inhibitor				
Bortezomib	*N/A*	0 / 126 (0.00%)	40 / 36,804 (0.11%)	0.7112

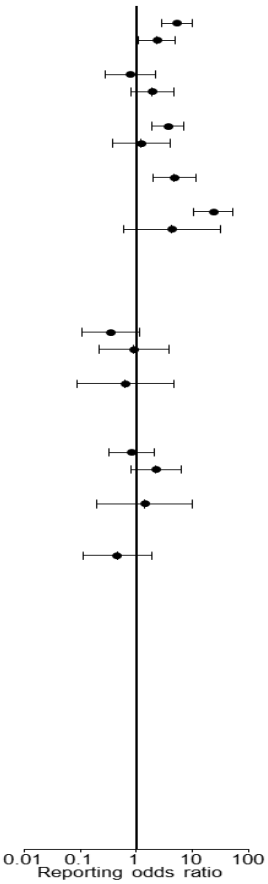

Figure S10. Reporting odds ratios for myelodysplastic syndrome in non-small cell lung cancer. VEGF, vascular endothelial growth factor; ALK, anaplastic lymphoma kinase; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Cisplatin	0.31 (0.07-1.37)	2 / 1,198 (0.17%)	12 / 2,211 (0.54%)	0.1014
Oxaliplatin	2.28 (0.63-8.20)	3 / 366 (0.82%)	11 / 3,043 (0.36%)	0.1953
Carboplatin	0.69 (0.09-5.30)	1 / 341 (0.29%)	13 / 3,068 (0.42%)	0.7208
Antimetabolites				
Fluorouracil	4.93 (1.54-15.7)	10 / 1,153 (0.87%)	4 / 2,256 (0.18%)	***0.0029***
Capecitabine	1.28 (0.36-4.60)	3 / 600 (0.50%)	11 / 2,809 (0.39%)	0.7063
Taxanes				
Paclitaxel	*N/A*	0 / 510 (0.00%)	14 / 2,899 (0.48%)	0.1158
Docetaxel	*N/A*	0 / 494 (0.00%)	14 / 2,915 (0.48%)	0.1227
Topoisomerase inhibitor				
Irinotecan	*N/A*	0 / 297 (0.00%)	14 / 3,112 (0.45%)	0.2467
Anthracycline				
Epirubicin	*N/A*	0 / 148 (0.00%)	14 / 3,261 (0.43%)	0.4244
Molecular targeted drugs				
EGFR inhibitor				
Cetuximab	*N/A*	0 / 216 (0.00%)	14 / 3,193 (0.44%)	0.3295
Erlotinib	*N/A*	0 / 101 (0.00%)	14 / 3,308 (0.42%)	0.5124
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 186 (0.00%)	14 / 3,223 (0.43%)	0.3677
Immune checkpoint inhibitors				
Nivolumab	*N/A*	0 / 139 (0.00%)	14 / 3,270 (0.43%)	0.4395

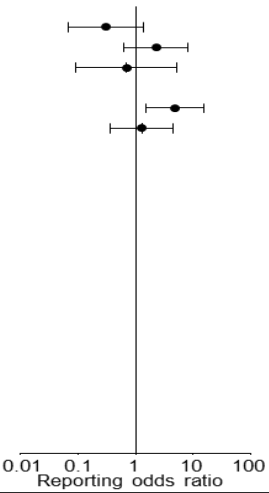

Figure S11. Reporting odds ratios for leukemia in esophageal cancer. EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Cisplatin	1.39 (0.48-4.00)	6 / 1,198 (0.50%)	8 / 2,211 (0.36%)	0.5446
Oxaliplatin	*N/A*	0 / 366 (0.00%)	14 / 3,043 (0.46%)	0.1935
Carboplatin	0.69 (0.09-5.30)	1 / 341 (0.29%)	13 / 3,068 (0.42%)	0.7208
Antimetabolites				
Fluorouracil	11.85 (2.65-53.1)	12 / 1,153 (1.04%)	2 / 2,256 (0.09%)	***<0.0001***
Capecitabine	0.36 (0.05-2.75)	1 / 600 (0.17%)	13 / 2,809 (0.46%)	0.3032
Taxanes				
Paclitaxel	0.44 (0.06-3.34)	1 / 510 (0.20%)	13 / 2,899 (0.45%)	0.4112
Docetaxel	*N/A*	0 / 494 (0.00%)	14 / 2,915 (0.48%)	0.1227
Topoisomerase inhibitor				
Irinotecan	0.81 (0.10-6.18)	1 / 297 (0.34%)	13 / 3,112 (0.42%)	0.8347
Anthracycline				
Epirubicin	*N/A*	0 / 148 (0.00%)	14 / 3,261 (0.43%)	0.4244
Molecular targeted drugs				
EGFR inhibitor				
Cetuximab	*N/A*	0 / 216 (0.00%)	14 / 3,193 (0.44%)	0.3295
Erlotinib	*N/A*	0 / 101 (0.00%)	14 / 3,308 (0.42%)	0.5124
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 186 (0.00%)	14 / 3,223 (0.43%)	0.3677
Immune checkpoint inhibitors				
Nivolumab	*N/A*	0 / 139 (0.00%)	14 / 3,270 (0.43%)	0.4395

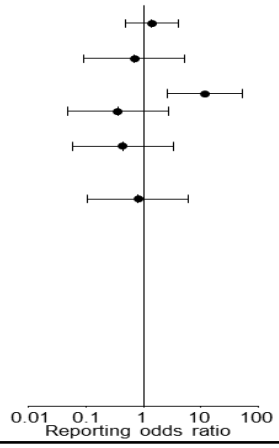

Figure S12. Reporting odds ratios for myelodysplastic syndrome in esophageal cancer. EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of leukemia with the anticancer drug	Incidence of leukemia without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Cisplatin	2.85 (0.83-9.78)	7 / 694 (1.01%)	4 / 1,124 (0.36%)	0.0812
Carboplatin	4.21 (1.28-13.9)	6 / 407 (1.47%)	5 / 1,411 (0.35%)	***0.0103***
Taxane				
Paclitaxel	2.32 (0.71-7.63)	6 / 622 (0.96%)	5 / 1,196 (0.42%)	0.1540
Antimetabolites				
Fluorouracil	5.27 (1.38-20.1)	3 / 123 (2.44%)	8 / 1,695 (0.47%)	***0.0066***
Topoisomerase inhibitors				
Topotecan	*N/A*	0 / 102 (0.00%)	11 / 1,716 (0.64%)	0.4173
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 432 (0.00%)	11 / 1,386 (0.79%)	0.0633

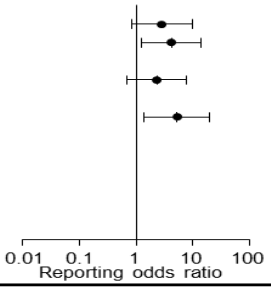

Figure S13. Reporting odds ratios for leukemia in cervical cancer. VEGF: vascular endothelial growth factor

Anticancer drug	Reporting odds ratio (95% confidence interval)	Incidence of myelodysplastic syndrome with the anticancer drug	Incidence of myelodysplastic syndrome without the anticancer drug	*p* value
Cytotoxic agents				
Platinums				
Cisplatin	*N/A*	3 / 694 (0.43%)	0 / 1,124 (0.00%)	***0.0274***
Carboplatin	*N/A*	3 / 407 (0.74%)	0 / 1,411 (0.00%)	***0.0012***
Taxane				
Paclitaxel	*N/A*	3 / 622 (0.48%)	0 / 1,196 (0.00%)	***0.0163***
Antimetabolites				
Fluorouracil	28.00 (2.52-311.0)	2 / 123 (1.63%)	1 / 1,695 (0.06%)	***<0.0001***
Topoisomerase inhibitors				
Topotecan	8.49 (0.76-94.4)	1 / 102 (0.98%)	2 / 1,716 (0.12%)	***0.0368***
Molecular targeted drugs				
VEGF inhibitor				
Bevacizumab	*N/A*	0 / 432 (0.00%)	3 / 1,386 (0.22%)	0.3332

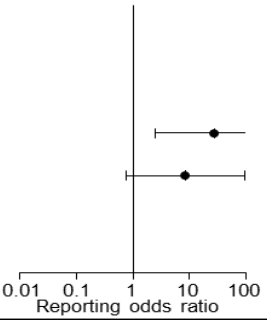

Figure S14. Reporting odds ratios for myelodysplastic syndrome in cervical cancer. VEGF: vascular endothelial growth factor