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Review Paper

Radiotherapy and Chemotherapy-Induced Myelodysplasia Syndrome

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Abbreviations: AML acute myeloid leukemia, CI = confidence interval, CT = chemotherapy, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, MDS = myelodysplastic syndrome, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute (NHRI), OR = odds ratio, RT = radiotherapy.
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ABSTRACT

This study explored which kinds of cancer are related to a higher incidence of subsequent myelodysplastic syndrome (MDS) after radiotherapy (RT) and chemotherapy (CT). We performed a nested case–control study by using data from the Taiwanese National Health Insurance (NHI) system. The case group included cancer patients who developed MDS. For the control group, 4 cancer patients without MDS were frequency-matched with each MDS case by age, sex, year of cancer diagnosis, and MDS index year. Overall, cancer patients who received RT or CT exhibited secondary MDS more frequently than did those who did not (RT: OR¼ 1.53; 95% CI¼ 1.33–1.77; CT: OR¼ 1.51; 95% CI¼ 1.25–1.82). Analysis by cancer site showed that RT increased the risk of MDS for patients with stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers. The major limitation of this study was the lack of certain essential data in the NHI Research Database, such as data regarding cancer stage and treatment dose details. This population-based nested case–control study determined that RT and CT predisposed patients in Taiwan to the development of MDS. This effect was more prominent when both modalities were used.

INTRODUCTION

In Taiwan, cancer has been the leading cause of death among the general population since 1982. The age-adjusted incidence rate has increased steadily since then; and it reached 320.65 new cases per 100,000 people in 2011.1 The proportion of long-term cancer survivors is rising owing to successful cancer-screening programs, earlier detection, advanced diagnostic tools, timely and effective treatment, improved follow-up after treatment, and an aging population.2 Consequently, the surveillance and monitoring of

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cancer survivors has become a crucial concern, regarding cancer control, as well as the emergence of cancer- and treatment-related health problems.3 Myelodysplastic syndrome (MDS) comprises a heterogeneous group of closely related clonal hematopoietic disorders that are characterized by hypocellular or hypercellular marrow with impaired morphology and maturation and peripheral blood cytopenias, followed by progressive impairment of the ability of myelodysplastic stem cells to differentiate and a tendency to evolve into acute myeloid leukemia (AML).4–6 MDS has been identified to be associated with previous cancer treatment by using chemotherapy (CT) or radiotherapy (RT). Treatmentrelated MDS has been reported in various cancers, such as breast cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, endometrial cancer, ovarian cancer, prostate cancer, and brain tumors. To the best of our knowledge, no nationwide populationbased study has measured treatment-related MDS for cancer overall and for various individual cancers. We explored this topic in Taiwan. We designed this research to determine, among cancer survivors, which primary sites of cancer were more susceptible to the development of MDS after treatment, and whether CT and RT interact. We used a database from the National Health Insurance (NHI) system of Taiwan to conduct this study.

METHODS

Data source

Taiwan has implemented the NHI program since 1995 and approximately 99% of the population (N ¼ 23.74 million) is currently enrolled in the program.14 This retrospective nested case–control study used the Longitudinal Health Insurance Database 2000 (LHID2000), a part of the National Health Insurance Research Database (NHIRD); the database was established and is maintained by the National Health Research Institutes (NHRI). The LHID2000 consists of claims data from 1,000,000 individuals randomly sampled (approximately 4.5% of Taiwan's population) from the registry of the NHIRD in 2000. There were no statistically significant differences in the distribution of sex, age, or health-care costs between the cohorts in the LHID2000 and insurance enrollees overall as reported by the NHRI in Taiwan.

Sampled Participants

A nested case–control study based on the LHID2000 was conducted. We identified patients in the Registry for Catastrophic Illness Database who were 20 years of age and older and had been newly diagnosed with primary cancer with the ICD-9-CM codes 140–195 and 200–208, not including AML and chronic myeloid leukemia (ICD-9-CM codes 205.0 and 205.10, respectively) between January 1, 2000 and December 31, 2011; these patients comprised the exposure cohort. We excluded patients with a history of MDS before 2000 and patients with a history of MDS before the diagnosis of cancer.

Potential Comorbidities and Treatments Associated With MDS

The diseases considered comorbidities included diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM code 401- 405), hyperlipidemia (ICD-9-CM code 272), stroke (ICD-9- CM codes 430–438), ischemic heart disease (ICD-9-CM codes 410–414), chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), and alcoholic liver damage (ICD-9-CM codes 571.0, 571.1, and 571.3). We also considered anticancer drugs and included alkylating agents, topoisomerase II inhibitors, and antimetabolites which are suggested to have increased risks of MDS two kinds of treatment before the index date were examined for their possible association with MDS: RT and CT.

Statistical Analysis

The baseline distributions of demographic characteristics, comorbidities, and treatments between MDS group and non-MDS group were compared using the x2 test for categorical variables and the t test for continuous variables. Univariable and multivariable unconditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between MDS and RT and CT. The multivariable models were simultaneously adjusted for the comorbidities of diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, and anticancer drugs

RESULTS

Table 1 shows a comparison of distributions of demographic characteristics, baseline comorbidities, and treatments between the MDS and the non-MDS groups. Among the 1265 patients with MDS, 50.8% of them were women and most were older than 65 years of age (56.1%). The mean ages of the MDS and non-MDS groups were 65.2 (SD ¼ 14.8) and 65.2 (SD ¼ 14.8) years, respectively. Compared with the non-MDS group, the MDS group patients were more likely to have diabetes, stroke, ischemic heart disease, chronic obstructive pulmonary disease, alcoholism, alkylating agents use, topoisomerase II inhibitors use, and antimetabolites use (all $P < 0.05$). The results of the multivariable logistic regression models for the association of RT and CT with MDS risk among patients with cancer are shown in Table 2Patients with diabetes, stroke, ischemic heart disease, alkylating agents use, and topoisomerase II inhibitors use also demonstrated a significant association with increased MDS risk. Furthermore, we estimated the risk of MDS following treatment with RT and CT for patients with various types of cancer (Table 3). Compared with stomach cancer patients who did not receive RT, stomach cancer patients who received RT were at a much higher risk of MDS. Similar results were observed for patients with colorectal, liver, female breast, prostate, and kidney cancers; for all of these, receiving RT increased the risk of MDS. Compared with lung cancer patients who did not receive CT, lung cancer patients who received CT had a 2.67-fold risk of MDS. Similar results were observed for cervical cancer patients; for all of these, CT increased the risk of MDS. Colorectal cancer patients who received alkylating agents treatment and topoisomerase II inhibitors treatment had higher risks of MDS compared with those who did not receive alkylating agents treatment and topoisomerase II inhibitors treatment (adjusted OR ¼ 4.49, 95% CI ¼ 1.29–15.6 and adjusted OR ¼ 24.2, 95% CI ¼ 2.63–222.9, respectively) (Table 4). Compared with head and neck cancer patients who did not receive alkylating agent treatment, head and neck cancer patients who received alkylating agent treatment were at a much higher risk of MDS. Compared with cervix cancer patients who did not receive topoisomerase II inhibitor treatment, cervical cancer patients who received topoisomerase II inhibitor treatment had a higher risk of MDS. Table 5 illustrates the joint effect of RT and CT on MDS risk. Compared with endometrial cancer patients who did not receive RT and CT, endometrial cancer patients who received both RT and CT had a higher risk of MDS (adjusted OR ¼ 37.0, 95% CI ¼ 2.96–462.4). Compared with lung cancer patients who did not receive RT and CT, lung cancer patients who received both RT and CT demonstrated a higher risk of MDS (adjusted OR ¼ 3.62, 95% CI ¼ 1.33–9.85). Similar results were observed for colorectal cancer, female breast cancer, and cervical cancer patients; receiving both RT and CT had a higher risk of MDS.

Table 1. Baseline Characteristics Between Myelodysplastic Syndrome Group and Non-Myelodysplastic Syndrome Group.

	Myelodysplastic syndrome				
	No N = 5057		Yes N=1265		P value
	N	%	n	%	
Gender					0.99
Women	2572	(50.9)	643	(50.8)	
Men	2485	(49.1)	622	(49.2)	
Age group(y)					0.99
20–49	880	(17.4)	220	(17.4)	
50-64	1344	(26.6)	336	(26.6)	
65-74	1284	(25.4)	321	(25.4)	
>75	1549	(30.6)	388	(30.7)	
Mean (SD) (y)	65.2	(14.8)	65.2	(14.8)	0.87
Baseline comorbidities					
Diabetes	850	(16.8)	254	(20.1)	0.006
Hypertension	2516	(49.8)	652	(51.5)	0.26
Hyperlipidemia	1281	(25.3)	290	(22.9)	0.08
Stroke	393	(7.77)	131	(10.4)	0.003
Ischemic heart disease	1283	(25.4)	392	(31.0)	<0.001
Chronic obstructive pulmonary disease	1977	(39.1)	550	(43.5)	0.004
Alcoholism	75	(1.48)	31	(2.45)	0.02
Alcoholic liver damage	105	(2.08)	33	(2.61)	0.25
Treatment					
Radiotherapy	1205	(23.8)	443	(35.0)	<0.001
Chemotherapy	1507	(29.8)	542	(42.9)	<0.001
Anti-cancer drugs					
Alkylating agents	571	(11.3)	233	(18.4)	<0.001
Topoisomerase II inhibitors	582	(11.5)	235	(18.6)	<0.001
Antimetabolites	1300	(25.7)	393	(31.1)	<0.001

TABLE 2. ORs and 95% CIs of Myelodysplastic Syndrome Associated With RT, CT, and Covariates.

Variable	Crude		Adjusted	
	OR	(95% CL)	OR	(95% CL)
Gender (women vs men)	1.00	(0.89,1.13)	_	_
Age group(y)	1.00	(1.00,1.01)	-	-
Baseline comorbidities				
Diabetes	1.24	(1.06,1.45)	1.21	(1.03,1.42)
Hypertension	1.07	(0.95,1.22)	-	-
Hyperlipidemia	0.88	(0.76,1.01)	-	-

Stroke	1.37	(1.11,1.69)	1.30	(1.05,1.62)
Ischemic heart disease	1.32	(1.15,1.51)	1.34	(1.15,1.56)
Chronic obstructive pulmonary disease	1.20	(1.06,1.36)	1.13	(0.99,1.30)
Alcoholism	1.67	(1.09,2.55)	1.54	(1.00,2.38)
Alcoholic liver damage	1.26	(0.85,1.88)		-
Treatment				
RT	1.72	(1.51,1.97)	1.53	(1.33,1.77)
CT	1.77	(1.56,2.00)	1.51	(1.25,1.82)
Anti-cancer drugs				
Alkylating agents	1.77	(1.50,2.10)	1.27	(1.02,1.57)
Topoisomerase II inhibitors	1.75	(1.49,2.07)	1.27	(1.03,1.55)
Antimetabolites	1.30	(1.14,1.49)	0.91	(0.77,1.08)

Table 3. ORs and 95% CIs of Myelodysplastic Syndrome Associated With RT, CT, and Covariates in Subdivision Cancer

			RT		CT	
			No	Yes	No	Yes
Cancer (ICD-9-CM)	**No of myelodysplastic syndrome/No of RT**	**No of myelodysplastic syndrome/No of CT**	**Adjusted OR (95%CI)**		**Adjusted OR (95%CI)**	
Head and neck (140–149, 161)	50/243	68/355	1.00 (Reference)	1.41 (0.80, 2.48)	1.00 (Reference)	1.11 (0.50, 2.49)
Esophagus (150)	11/47	11/38	1.00 (Reference)	0.84 (0.21, 3.33)	1.00 (Reference)	1.53 (0.18, 12.7)
Stomach (151)	12/22	34/92	1.00 (Reference)	2.76 (1.06, 7.19)	1.00 (Reference)	1.72(0.80, 3.71)
Colorectum (153–154)	30/131	60/335	1.00 (Reference)	.94 (1.16, 3.23)	1.00 (Reference)	1.63 (0.94, 2.83)
Liver (155)	14/43	15/86	1.00 (Reference)	2.57 (1.22, 5.38)	1.00 (Reference)	0.92 (0.43, 1.97)
Lung (162)	25/130	38/177	1.00 (Reference)	1.32 (0.69, 2.52)	1.00 (Reference)	2.67 (1.07, 6.67)
Female breast (174)	54/257	75/452	1.00 (Reference)	1.86 (1.20, 2.89)	1.00 (Reference)	1.87 (0.71, 4.95)
Uterus/endometrium (179, 182)	13/45	7/16	1.00 (Reference)	3.16 (1.05, 9.49)	1.00 (Reference)	7.59 (1.07, 53.6)

Cervix (180)	50/179	38/99	1.00 (Reference)	1.44 (0.77, 2.69)	1.00 (Reference)	2.41 (1.16, 5.00)
Prostate (185)	39/129	13/31	1.00 (Reference)	2.12 (1.22, 3.67)	1.00 (Reference)	1.61 (0.63, 4.12)
Bladder (188)	8/24	18/55	1.00 (Reference)	0.98 (0.28, 3.41)	1.00 (Reference)	1.26 (0.48, 3.34)
Brain tumor (191)	7/38	3/8	1.00 (Reference)	0.18 (0.02, 2.18)	1.00 (Reference)	12.3 (0.38, 403.4)
Kidney (189)	8/12	13/28	1.00 (Reference)	5.59 (1.36, 23.1)	1.00 (Reference)	1.31 (0.20, 8.44)
Non-Hodgkin lymphoma (202)	14/42	23/86	1.00 (Reference)	0.91 (0.33, 2.53)	1.00 (Reference)	0.27 (0.04, 1.65)
Lymphoblastic l eukemia (204)	3/7	4/8	1.00 (Reference)	2.88 (0.02, 339.9)	1.00 (Reference)	0.08 (0.02, 3.37)
Myeloid leukemia (205)	23/28	33/44	1.00 (Reference)	3.12 (0.75, 12.9)	1.00 (Reference)	2.04 (0.19, 22.4)

Table 4. ORs and 95% CIs of myelodysplastic syndrome associated with anticancer drugs and covariates in subdivision cancer

	Alkylating agents		**Topoisomerase II inhibitors**		**Antimetabolites**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
Cancer (ICD-9-CM)	**Adjusted OR (95%CI)**		**Adjusted OR (95%CI)**		**Adjusted OR (95%CI)**	
Head and neck (140–149, 161)	1.00 (Reference)	7.08 (2.35,21.3)	1.00 (Reference)	0.43 (0.09,2.05	1.00 (Reference)	1.61 (0.76, 3.41)
Esophagus (150)	1.00 (Reference)	2.15 (0.19, 24.2)	1.00 (Reference)	1.42 (0.12, 16.6)	1.00 (Reference)	1.01 (0.14, 7.45)
Stomach (151)	1.00 (Reference)	0.66 (0.16, 2.71)	1.00 (Reference)	1.18 (0.42, 3.33)	1.00 (Reference)	0.95 (0.50, 1.81)
Colorectum (153–154)	1.00 (Reference)	4.49 (1.29, 15.6)	1.00 (Reference)	24.2 (2.63, 222.9)	1.00 (Reference)	0.94 (0.56, 1.57)
Liver (155)	1.00 (Reference)	10.8 (0.46, 253.3)	1.00 (Reference)	0.90 (0.48, 1.69)	1.00 (Reference)	1.38 (0.55, 3.48)
Lung (162)	1.00 (Reference)	0.44 (0.05, 3.88)	1.00 (Reference)	0.92 (0.34, 2.47)	1.00 (Reference)	1.35 (0.60, 3.02)

Female breast (174)	1.00 (Reference)	0.83 (0.31, 2.23)	1.00 (Reference)	1.14 (0.66, 1.99)	1.00 (Reference)	0.70 (0.39, 1.26)
Uterus/endometrium (179, 182)	1.00 (Reference)	2.08 (0.15, 29.3)	1.00 (Reference)	0.06 (0.00, 1.000	1.00 (Reference)	0.85 (0.34, 23.6)
Cervix (180)	1.00 (Reference)	2.79 (0.89, 8.78)	1.00 (Reference)	10.5 (1.05, 105.1)	1.00 (Reference)	1.05 (0.41, 2.71)
Prostate (185)	1.00 (Reference)	-	1.00 (Reference)	2.93 (0.13, 68.4)	1.00 (Reference)	3.98 (0.93, 17.1)
Bladder (188)	1.00 (Reference)	9.94 (0.63, 157.5)	1.00 (Reference)	1.80 (0.82, 3.95)	1.00 (Reference)	12.0 (2.81, 51.5)
Brain tumor (191)	1.00 (Reference)	10.9 (0.67, 179.1)	1.00 (Reference)	-	1.00 (Reference)	0.22 (0.00, 23.7)
Kidney (189)	1.00 (Reference)	0.55 (0.02, 16.8)	1.00 (Reference)	4.25 (0.62, 29.2)	1.00 (Reference)	0.83 (0.14, 4.81)
Non-Hodgkin lymphoma (202)	1.00 (Reference)	1.21 (0.24, 5.98)	1.00 (Reference)	1.40 (0.36, 5.55)	1.00 (Reference)	7.49 (2.21, 25.3)
Lymphoblastic leukemia (204)	1.00 (Reference)	5.94 (0.55, 64.3)	1.00 (Reference)	1.92 (0.03, 143.4)	1.00 (Reference)	-
Myeloid leukemia (205)	1.00 (Reference)	0.73 (0.17, 3.11)	1.00 (Reference)	0.81 (0.14, 4.52)	1.00 (Reference)	0.66 (0.05, 8.98)

Table 5. ORs and 95% CIs of myelodysplastic syndrome associated radiotherapy with joint effect of chemotherapy.

Variables		**No of myelodysplastic syndrome**		**Alkylating agents**	**Topoisomerase II inhibitors**	**Antimetabolites**
		No	**Yes**	**(95%CI) Adjusted OR**	**(95%CI) Adjusted OR**	**(95%CI) Adjusted OR**
Colorectasl cancer						
Radiotherapy	Chemotherapy					
No	No	610	69	1 (Reference)		
No	Yes	204	39	1.87 (1.04, 3.38)	1 (Reference)	
Yes	No	30	9	2.93 (1.30, 6.60)	-	1 (Reference)
Yes	Yes	71	21	2.89 (1.39, 6.00)	1.79 (0.93, 3.48)	1.62 (0.44, 6.00)

Liver cancer						
Radiotherapy	Chemotherapy					
No	No	325	53	1 (Reference)		
No	Yes	59	11	1.14 (0.51, 2.55)	1 (Reference)	
Yes	No	17	10	3.48 (1.47, 8.24)	-	1 (Reference)
Yes	Yes	12	4	1.39 (0.36, 5.35)	1.48 (0.24, 9.17)	0.17 (0.02, 2.01)
Lung cancer						
Radiotherapy	Chemotherapy					
No	No	122	10	1 (Reference)		
No	Yes	68	17	2.90 (1.00, 8.39)	1 (Reference)	
Yes	No	34	4	1.55 (0.45, 5.34)	-	1 (Reference)
Yes	Yes	71	21	3.62 (1.33, 9.85)	1.24 (0.58, 2.64)	1.60 (0.40, 6.44)
Female breast cancer						
No	No	257	31	1 (Reference)		
No	Yes	217	30	1.75 (0.63, 4.87)	1 (Reference)	
Yes	No	43	9	1.61 (0.70, 3.68)	-	1 (Reference)
Yes	Yes	160	45	3.46 (1.28, 9.33)	1.93 (1.13, 3.29)	3.60 (0.92, 14.1)
Uterine/endometrail cancer						
Radiotherapy	Chemotherapy					
No	No	55	8	1 (Reference)		
No	Yes	4	2	3.15 (0.21, 47.6)	1 (Reference)	
Yes	No	27	8	2.63 (0.81, 8.49)	-	1 (Reference)
Yes	Yes	5	5	37.0 (2.96, 462.4)	1.70 (0.13, 21.6)	3.21 (0.72, 14.3)
Cervical cancer						
Radiotherapy	Chemotherapy					
No	No	209	31	1 (Reference) 2.43 (1.09, 5.44)		
No	Yes	6	4	1.45 (0.26, 8.19)	1 (Reference)	
Yes	No	74	16	1.32 (0.67, 2.62)	-	1 (Reference)

Yes	Yes	55	34	3.46 (1.79, 6.65)		

DISCUSSION

The results from this population-based nested case– control study highlighted the fact that overall cancer treatment with either RT or CT can significantly increase the risk of subsequently developing MDS. Analysis by cancer site indicated that patients with stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers after RT had a significantly high risk of developing MDS. MDS is not uncommon. Approximately 20,000 cases of MDS were diagnosed in the United States in 2008, of which approximately 10% were therapy related.15 From our NHI database, 454 cases of MDS were diagnosed in Taiwan in 2008. The prognosis of MDS is relatively poor, Traditional cancer therapy operates by producing extensive DNA damage that in turn inhibits proliferation and activates cell-death pathways. People accidentally exposed to ionizing radiation, as well as cancer patients receiving RT, have been extensively linked to hematological malignancies.18–20 By contrast, alkylating agents, topoisomerase II inhibitors, and antimetabolites are frequently cited perpetrators of CT-induced MDS.13,15 Alkylating agents comprise a large group of anticancer drugs with clinical applications across almost all types of cancer. Our results showed that breast cancer survivors who received RT are more vulnerable to developing MDS compared with their counterparts, but not breast cancer survivors who received CT (Table 3). When we used breast cancer patients without RT and CT as the reference, neither the RT nor the CT group showed a significantly higher risk of MDS, but the group treated with both RT and CT did manifest a significantly higher risk of MDS (Table 5, OR ¼ 3.46; 95% CI ¼ 1.28–9.33). They suggested that using RT to treat breast cancer is associated with an increased risk of MDS/AML and affects an extremely small number of patients.27 It is reasonable that there have been more reports of MDS development among breast cancer survivors compared with other cancer survivors. Because of the relative success of cancer screening programs, early detection and timely and appropriate treatment have yielded more favorable prognoses for patients with breast cancer compared with patients with most other types of cancer. More survivors of prostate cancer can be expected compared with other cancers. RT is one of the major therapies for prostate cancer, but CT does not play a crucial role in the treatment of prostate cancerThe association between CT and MDS in prostate cancer was not that obvious because of the relatively small number of patients receiving CT (Table 3). Hematological malignancies were also studied to determine the association between cancer treatment and subsequent MDS.13,29,30 The present study failed to find any significant relationship between cancer treatment and MDS in these malignancies except for antimetabolites users among non-Hodgkin lymphoma with a higher MDS risk (Table 4 We subclassified CT into alkylating agent, topoisomerase II inhibitors, and antimetabolites to analyze because they are suggested to have increased risks of MDS.13 Tebbi et al found a novel association between topoisomerase inhibition and risk of secondary myeloid neoplasms in pediatric Hodgkin disease..35 Le Deley et al found that the risk of MDS is much higher with mitoxantrone-based CT than with anthracycline-based CT in breast cancer patients.20 Users of topoisomerase II inhibitors were found to have significantly higher risks for MDS among colorectal cancer and cervical cancer patients in our study. Antimetabolites, and in particular the immunosuppressive agents

azathioprine and fludarabine, have also been associated with MDS.9 Our data revealed that antimetabolite users had significantly higher risks of MDS among bladder cancer and non-Hodgkin lymphoma patients. A tendency of a positive joint effect of RT and CT was observed in our study. As shown in Table 5, a reference group of patients who did not receive RT or CT exhibited the joint effect of both treatments in lung, breast, endometrial, and cervical cancers. In these cancer sites, double-treatment groups, but not single-treatment groups, had significantly higher risks of MDS. When used single-treatment group as the reference, Table 5 also revealed consistent higher adjusted ORs of double-treatment group compared with single-treatment group (except for liver cancer), although P values seldom reached the significant level due to small case number. The positive interaction between RT and CT was observed in an early study conducted by Smith et al, who indicated that among patients receiving adjuvant CT for breast cancer, the risk of MDS increases with age, with the intensity of therapy, and with the use of breast RT.28 This implied that a synergistic effect of MDS may exist between RT and CT. Combining RT and CT (either concurrent or sequential) in cancer treatment has been proven to increase therapeutic results in several cancers.36–40 Treatment-related toxicity may be also additive.41–43 Therefore, combination therapy may confer a higher risk of MDS. In conclusion, this population-based nested case–control study found that both RT and CT are related to the subsequent development of MDS. Some cancer sites are more susceptible to developing MDS after cancer treatment. which far outweigh the potential risk of MDS.

REFERENCES

1. Cancer Statistics Annual Report: Taiwan Cancer Registry. Available from http://tcr.cph.ntu.edu.tw/main.php?Page=N2. Accessed September 25, 2014.
2. Pollack LA, Rowland JH, Crammer C, et al. Introduction: charting the landscape of cancer survivors' health-related outcomes and care. Cancer. 2009;115:4265–4269.
3. Choi M, Craft B, Geraci SA. Surveillance and monitoring of adult cancer survivors. Am J Med. 2011;124:598–601.
4. Cazzola M, Malcovati L. Myelodysplastic syndromes – coping with ineffective hematopoiesis. N Engl J Med. 2005;352:536–538.
5. Besa EC. Myelodysplastic syndromes (refractory anemia). A perspective of the biologic, clinical, and therapeutic issues. Med Clin North Am. 1992;76:599–617.
6. Germing U, Kobbe G, Haas R, et al. Myelodysplastic syndromes: diagnosis, prognosis, and treatment. Dtsch Arztebl Int. 2013;110:783–790.
7. Cole M, Strair R. Acute myelogenous leukemia and myelodysplasia secondary to breast cancer treatment: case studies and literature review. Am J Med Sci. 2010;339:36–40.
8. Leone G, Pagano L, Ben-Yehuda D, et al. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. 2007;92:1389–1398.
9. Bonin SR, Lanciano RM, Smith MR, et al. Treatment-related myelodysplastic syndrome following abdominopelvic radiotherapy for endometrial cancer. Gynecol Oncol. 1995;57:430–432.
10. Mukherjee S, Reddy CA, Ciezki JP, et al. Risk for developing myelodysplastic syndromes in prostate cancer patients definitively treated with radiation. J Natl Cancer Inst. 2014;106:djt462.
11. Sugiyama K, Kurisu K, Arita K, et al. Myelodyeplastic syndrome following therapy for brain tumor – two case reports. Neurol Med Chir (Tokyo). 2002;42:170–174.

12. Sill H, Olipitz W, Zebisch A, et al. Therapy-related myeloid neoplasms: pathobiology and clinical characteristics. Br J Pharmacol. 2011;162:792–805.
13. Graubert T. Therapy-related myelodysplastic syndrome: models and genetics. Biol Blood Marrow Transplant. 2010;16:S45–S47.
14. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51:189–199.
15. Grossi A, Liumbruno GM. New drugs in the treatment of myelodysplastic syndromes: are they changing the role of transfusion support? Blood Transfus. 2008;6:191–198.
16. Ojha RP, Fischbach LA, Zhou Y, et al. Acute myeloid leukemia incidence following radiation therapy for localized or locally advanced prostate adenocarcinoma. Cancer Epidemiol. 2010;34:274– 278.
17. Warlick ED, Smith BD. Myelodysplastic syndromes: review of pathophysiology and current novel treatment approaches. Curr Cancer Drug Targets. 2007;7:541–558Review.
18. Rund D, Ben Yehuda D. Therapy-related leukemia and myelodysplasia: evolving concepts of pathogenesis and treatment. Hematology. 2004;9:179–187.
19. Pedersen-Bjergaard J, Andersen MK, Christiansen DH, et al. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. Blood. 2002;99:1909–1912.
20. Moloney WC. Radiogenic leukemia revisited. Blood. 1987;70:905– 908.
21. Leleu X, Soumerai J, Roccaro A, et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenstrom macroglobulinemia treated with nucleoside analogs. J Clin Oncol. 2009;27:250–255.

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