J Chin Med Assoc

ORIGINAL ARTICLE

Hematologic adverse drug reactions leading to hospitalization among cancer patients: A retrospective case-control study

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Abstract

Background: Cancer is one of the leading causes of death worldwide. Despite the rapid evolution of cancer treatment, chemotherapy remains the mainstay in the management of cancer. Chemotherapy can result in various adverse drug reactions (ADRs), which may lead to hospitalization and even life-threatening side-effects. Hematologic ADRs are among the most severe forms of ADR following chemotherapy, as they generally lead to hospitalization. It is important to realize the predictors and outcome of hematologic ADRs in cancer patients.

Methods: We conducted a hospital-based case-control study to include all the cancer patients who were hospitalized to receive chemotherapy in Taipei Veterans General Hospital during 2013. Among them the patients rehospitalized after chemotherapy due to neutropenia, leucopenia, or pancytopenia were identified as the study group. Control subjects consisted of hospitalized cancer patients who did not display the aforementioned ADRs. The study and control groups were numbered in the ratio of 1:4 and were age- and gender-matched. Their demographic and clinical characteristics were collected through chart review. Determinants of hematologic ADRs were then analyzed.

Results: During the study period, we collected a total of 64 patients into the study group and 256 as control subjects. The mean length of hospitalization was 11 days in the study group of patients, which was 5 days longer than that in the control group ($p < 0.001$). Predictors of hematologic ADR-related hospitalization included history of hematologic ADRs, hypertension, cisplatin treatment, and a Charlson comorbidity score of 2 to 3.

Conclusion: Severe outcomes of hematologic ADRs may increase healthcare costs and decrease patient productivity. Therefore, the determinants of ADR-related hospitalization identified in this study may help improve the quality of healthcare for cancer patients.

Keywords: Cancer; Chemotherapy; Drug-related side effects and adverse reactions; Hospitalization; Neutropenia

1. INTRODUCTION

Cancer is one of the leading causes of death worldwide. In Taiwan, cancer has ranked as the leading cause of death for 32 consecutive years, according to the statistics from the Ministry of Health and Welfare. Despite the rapid evolution of cancer treatment options, chemotherapy remains the mainstay in the management of cancer. However, various adverse drug reactions (ADRs) as a result of chemotherapy often lead to hospitalization and even life-threatening side-effects.[1,2] Although previous studies have largely been conducted among elder populations who tended to suffer more chronic diseases requiring more complicated medications,[3,4] identification of the predictable risk factors in cancer patients, as has seldom been investigated, becomes very important not only to prevent hospitalization but also to more effectively allocate medical resources and expenditure.

Hematologic ADRs are probably the most severe one among the numerous ADRs following chemotherapy leading to hospitalization, but in Taiwan few studies have examined the hematologic ADRs among hospitalized cancer patients. The aims of the present study were therefore to find out the determinants as well as outcomes of neutropenia, leucopenia, and pancytopenia, because all of them are associated with decreased white blood cell count indicative of fatal complications or infections.

2. METHODS

2.1. Study population and setting

The study enrolled patients who were aged ≥20 years and admitted to Taipei Veteran General Hospital (TVGH) for chemotherapy with the diagnosis of any cancer coded by the *International*

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 784-790.

Received October 22, 2019; accepted February 13, 2020.

doi: 10.1097/JCMA.0000000000000298.

Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 140-239 in 2013 (**Fig. 1**). The ADR cases in this study were identified as the patients with diseases of white blood cells (ICD-9-CM 288.0), including neutropenia, leucopenia, or pancytopenia, diagnosed upon or during hospitalization. Patients were excluded from the study group if they had normal range of white blood cell counts (4500-11 000/mm^3), had no laboratory test, undertook no chemotherapy within 2 weeks before developing neutropenia/leukopenia/ pancytopenia, or were foreigners (non-Taiwanese). The control subjects were selected randomly from all hospitalized cancer patients who did not have hematologic ADRs (i.e., neutropenia, leucopenia, or pancytopenia). The study and control groups were numbered in the ratio of 1:4, and matched in age (±2 years) and gender. Many patients had more than one admission during the study period. For the study group, only the first hospitalization due to neutropenia, leucopenia, or pancytopenia (with or without fever) in 2013 was evaluated and the date of admission was defined as the "index date," whereas every control subject was selected by the index date of the study subject that they were matched to. If no control subject was admitted on the same date as their matched cases, the one admitted on the nearest date was selected. The study protocol was approved (No. 2014-10-010CC) by the Institutional Review Board of TVGH.

Hematologic ADR-related hospitalization was defined as the dependent variable, whereas the independent variables included cancer type and drug-related factors (such as types of chemotherapy drugs and number of combined chemotherapy drugs). Potential confounders were also analyzed, including sociodemographics (i.e., age, gender, body mass index [BMI], residence, identity, marital status, educational level, occupation, and lifestyle), clinical variables (i.e., history of hematologic ADRs, type of admission, comorbidities, Charlson Comorbidity Index [CCI] score, and preexisting data of lymphocyte counts), and outcomes of neutropenia, leucopenia, or pancytopenia (i.e., mean hospital stay, use of granulocyte colony-stimulating factor [G-CSF], and complications). Clinical variables collected from medical charts were age, gender, BMI, history of hematologic ADRs, route of admission, comorbidities, preexisting data of lymphocyte counts, length of hospital stay, complications, and types of cancer.

2.2. Statistical analysis

All statistical analyses were conducted by STATA 13.0. Descriptive and inferential analyses were both presented in this study. For categorical independent variables and potential confounders, chi-square test or Fisher's exact test was used to compare the baseline characteristics between the study group and the control group. Univariate and multivariate conditional logistic regression analyses were conducted to identify the predictors of neutropenia, leucopenia, and pancytopenia. All independent variables with a p value <0.2 in the bivariate analyses

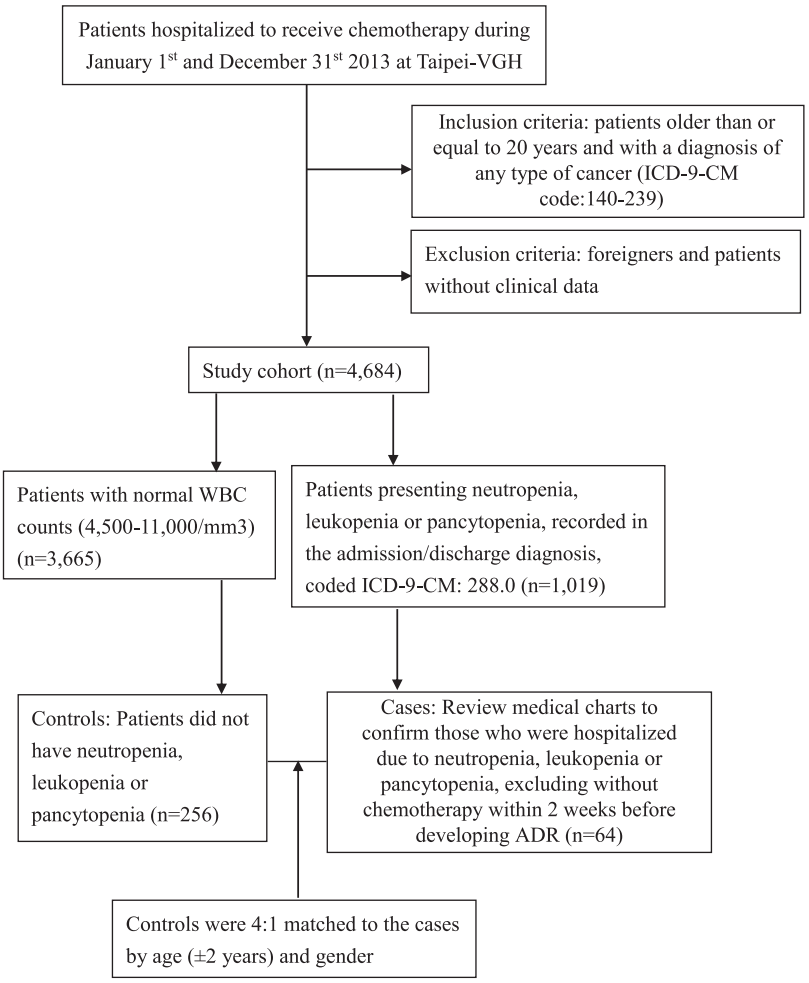

Fig. 1 Selection of the study cases and controls. ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; VGH = Veteran General Hospital; WBC = white blood cell; ADR = adverse drug reaction.

or univariate logistic regression analyses were put into the multivariate conditional logistic regression model and a stepwise approach was used to identify the final regression model. The results of both univariate and multivariate conditional logistic regression analyses were shown by crude and adjusted odds ratio (OR) and relevant 95% CIs. $p < 0.05$ was considered statistically significant.

3. RESULTS

Among a total of 4684 patients receiving chemotherapy during 2013 at TVGH, 1019 were coded with ICD-9-CM 288.0 as admission or discharge diagnosis. Within the 1019 potential cases, 64 eligible cases were identified, and 256 matched control subjects were then randomly selected from those who did not have hematologic ADRs.

3.1. Patient characteristics

Both the study and control groups were at a mean age of approximately 55 years with roughly equivalent gender distribution. The mean BMI was 23 kg/m^2 in the study group and 23.4 kg/m^2 in the control group, respectively (Table 1). Most patients were in the normal range of BMI; however, large minority of patients in both the study (40.6%) and control subjects (40.2%) were overweight. Most patients were nonsmokers and did not habitually drink alcohol or chew betel nuts. None of the sociodemographic characteristics showed significant difference between the study and control groups, either.

Table 1

Baseline sociodemographic characteristics

Characteristics	Case group (n = 64)	Control group (n = 256)	*p*
Age, mean ± SD, y	55.1 ± 15.8	55.2 ± 15.7	0.97
Male	31 (48.4%)	130 (50.8%)	1
BMI, mean ± SD, kg/m^2	23 ± 4.1	23.4 ± 4.2	0.686
Veteran status	5 (7.8%)	28 (10.9%)	0.462
Married	45 (70.3%)	181 (70.7%)	0.951
Employed	34 (53.1%)	129 (50.4%)	0.696
Cigarette smoking	4 (6.3%)	18 (7.1%)	1
Alcohol consumption	4 (6.3%)	24 (9.4%)	0.70
Betel nut chewing	2 (3.1%)	2 (0.8%)	0.18
History of hematologic ADR	60 (93.8%)	56 (21.9%)	<0.001*
Route of admission			<0.001*
Emergency department	15 (23.4%)	15 (5.9%)	
Outpatient clinic	49 (76.6%)	246 (94.1%)	
CCI score			0.074
2-3	27 (42.2%)	96 (37.5%)	
4-6	18 (28.1%)	109 (42.6%)	
≥7	19 (29.7%)	51 (19.9%)	
Comorbidities			
Heart disease	7 (10.9%)	21 (8.2%)	0.489
Liver disease	13 (20.3%)	34 (13.3%)	0.155
Ulcer disease	10 (15.6%)	23 (9%)	0.118
Renal disease	5 (7.8%)	15 (5.9%)	0.564
Hypertension	34 (53.1%)	70 (27.3%)	<0.001*
Diabetes mellitus	11 (17.2%)	35 (13.7%)	0.473
Hyperlipidemia	4 (6.3%)	11 (4.3%)	0.508
Metastasis of cancer	31 (48.4%)	121 (47.3%)	0.538
Lymphocyte count			0.009*
Normal	23 (35.9%)	127 (49.6%)	
Abnormal	41 (64.1%)	116 (45.3%)	
Data unknown	0 (0%)	13 (5.1%)	

ADR = adverse drug reaction; BMI = body mass index; CCI score = Charlson Comorbidity Index score.
*$p < 0.05$.

The bivariate analysis found that history of neutropenia/leukopenia/pancytopenia, route of admission, and presence of specific comorbidities and abnormal lymphocyte counts were the risk factors of hospitalization due to neutropenia, leucopenia, or pancytopenia. In the study group, 60 (93.8%) patients had at least one prior episode of neutropenia, leucopenia, or pancytopenia, in contrast to 56 control subjects (21.9%) presenting such ADR history ($p < 0.001$). Moreover, 15 patients (23.4%) in the study group were admitted to the hospital through the emergency department (ED), compared with 15 control subjects (5.9%) ($p < 0.001$). Compared with the control group, the study group had higher proportion of patients with heart disease, liver disease, peptic ulcer disease, renal disease, diabetes mellitus, hyperlipidemia, and metastasis of cancer, although the difference was not significant. The study group of patients tended to have more comorbidities and higher CCI scores than the control subjects ($p = 0.074$) did, but it showed no significant difference, either.

We found that 34 patients (53.1%) in the study group and 70 control subjects (27.3%) had hypertension ($p < 0.001$), and that 41 patients (64%) in the study group and 116 control subjects (45%) had abnormal values of lymphocyte counts before admission ($p = 0.009$). Moreover, hematologic tumor (including lymphomas and leukemia) was found in 14 patients (21.9%) in the study group, in contrast to 32 control subjects (12.5%) with hematologic tumor ($p = 0.056$). The number of chemotherapy drugs, however, was not significantly different between groups.

Seeing that cisplatin and 5-fluorouracil (5-FU) were the most widely used drugs in the study population, we categorized chemotherapy drugs into four types (Table 2). The first type of chemotherapy consisted of any treatment combination with cisplatin but not with 5-FU, the second type included any treatment combination with 5-FU but not with cisplatin, the third type comprised any combination with both cisplatin and 5-FU, and the last type consisted of all the other combinations without 5-FU or cisplatin. As a result, 24 cases (37.5%) in the study group and 56 controls (21.9%) were in the first type, 5 cases (7.8%) and 57 controls (22.3%) were in the second type, 7 cases (10.9%) and 21 controls (8.2%) were in the third type, and 28 cases (43.8%) and 122 controls (47.7%) were in the last type ($p = 0.011$).

3.2. Clinical outcomes

The mean hospital stay was 11 days in the study group, 5 days longer than that in the control group ($p = 0.002$) (Table 3). Most patients were discharged with complete recovery; however, two in the study group and four in the control group died during

Table 2

Cancer type and chemotherapy drug option

Variables	Case group (n = 64)	Control group (n = 256)	*p*
Type of cancer			0.056
Solid tumor	50 (78.1%)	224 (87.5%)	
Hematologic tumor	14 (21.9%)	32 (12.5%)	
Number of chemotherapy drugs			0.354
1	13 (20.3%)	75 (29.3%)	
2	39 (60.9%)	139 (54.3%)	
>3	12(18.8%)	42 (16.4%)	
Category of chemotherapy drugs			0.011*
Cisplatin without 5-FU	24 (37.5%)	(21.9%)	
5-FU without cisplatin	5 (7.8%)	57 (22.3%)	
5-FU + cisplatin	7 (10.9%)	21 (8.2%)	
Others	28 (43.8%)	122 (47.7%)	

5-FU = 5-fluorouracil.
*$p < 0.05$.

Table 3

Clinical outcomes

Variables	Case group (n = 64)	Control group (n = 256)	*p*
Days of hospital stay, mean ± SD	10.53 ± 12.8	5.85 ± 9.2	<0.001*
Use of G-CSF	40 (62.5%)	16 (6.3%)	<0.001*
Sepsis	8 (12.5%)	6 (2.3%)	<0.001*
Anemia	24 (40.6%)	28 (10.9%)	<0.001*
Thrombocytopenia	12 (18.7%)	6 (2.3%)	<0.001*
Fever	28 (43.7%)	25 (9.8%)	<0.001*
Infection	26 (40.6%)	33 (12.9%)	<0.001*

G-CSF = granulocyte colony-stimulating factor.
*$p < 0.05$.

hospitalization. The *p* values of all outcome variables except the vital status were <0.001 between the study and control groups; in other words, sepsis, anemia, thrombocytopenia, fever, and infection were all more likely to occur in patients who were hospitalized due to neutropenia, leucopenia, or pancytopenia. In addition, G-CSF was generally prescribed in the study group for treatment of chemotherapy-related neutropenia, leucopenia, or pancytopenia.

3.3. Risk factors of hematologic ADR-related hospitalization

In univariate conditional logistic regression analysis, the crude OR for route of admission, history of hematologic ADRs, hypertension, lymphocyte counts, cancer type, and types of chemotherapy drug administration were all statistically significant factors of hematologic ADR-related hospitalization (Table 4). Those who had at least one prior episode of neutropenia, leucopenia, or pancytopenia ran a 45 times higher risk to be hospitalized than those who never had that history (OR = 45.4, $p < 0.001$). Similarly, the patients with hypertension under treatment had a 3.9-fold higher risk (OR = 3.9, $p < 0.001$) of hospitalization than those without hypertension. In contrast, the second type of chemotherapy, combined with 5-FU but without cisplatin (OR = 0.2, $p = 0.003$), and the other combinations of chemotherapy drugs (OR = 0.54, $p = 0.05$) were less likely to render patients into hospitalization due to hematologic ADRs, as compared with the patients under cisplatin without 5-FU treatment.

Variables with $p \leq 0.2$ figured out by univariate conditional logistic regression analysis were put into multiple conditional logistic regression model. These variables included cancer type, types of chemotherapy drugs, route of admission, history of hematologic ADRs, hypertension, lymphocyte counts, betel nut chewing habit, comorbidities, liver disease, and peptic ulcer disease. The multiple conditional logistic regression model again identified the predictive risk factors of hematologic ADR-related hospitalization, including history of hematologic ADRs, hypertension, combination chemotherapy with cisplatin but without 5-FU, and CCI score 2 to 3. Those patients having at least one prior episode of neutropenia, leucopenia, or pancytopenia were 66 times more likely (OR = 65.9, $p < 0.001$) to be admitted due to hematologic ADRs, compared with those who never had that history. Patients with hypertension under treatment were four times more likely (OR = 4.3, $p = 0.011$) to be admitted for the aforementioned hematologic ADRs, compared with those without hypertension. Notably, patients under combination chemotherapy of 5-FU without cisplatin (OR = 0.1, $p = 0.017$), combination chemotherapy with both cisplatin and 5-FU (OR = 0.2, $p = 0.046$), and combination chemotherapy without 5-FU and cisplatin (OR = 0.3, $p = 0.024$) were all less likely to be admitted because of hematologic ADRs, as compared with those treated with cisplatin without 5-FU. Patients with CCI scored 2 to 3 had a higher risk of hospitalization

Table 4

Conditional logistic regression analysis of hematologic ADR-related risk factors

Variables	Crude OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Route of admission				
Outpatient clinic	Reference		...	...
Emergency department	4.8 (2.17, 10.47)	<0.001*	...	...
History of hematologic ADR				
No	Reference		Reference	
Yes	45.4 (14.01, 146.36)	<0.001*	65.9 (17.23, 252.18)	<0.001*
Hypertension				
No	Reference		Reference	
Yes	3.9 (2.02, 7.62)	<0.001*	4.3 (1.4, 12.98)	0.011*
Lymphocyte counts				
Abnormal	Reference		...	...
Normal	0.5 (0.27,0.78)	0.004*	...	...
Type of cancer				
Solid tumor	Reference		Reference	
Hematologic tumor	2.1 (1.01, 4.44)	0.046*	0.3 (0.07, 1.57)	0.168
Category of chemotherapy drugs				
Cisplatin (without 5-Fu)	Reference		Reference	
5-FU (without cisplatin)	0.2 (0.08, 0.6)	0.003*	0.1 (0.01, 0.66)	0.017*
5-FU + cisplatin	0.8 (0.29, 2.12)	0.635	0.2 (0.03, 0.97)	0.046*
Others	0.5 (0.29, 1)	0.05*	0.3 (0.11, 0.86)	0.024*
CCI score				
2-3	Reference		Reference	
4-6	0.6 (0.31, 1.18)	0.139	0.2 (0.07, 0.73)	0.013*
≥7	1.4 (0.65, 2.8)	0.421	...	...

ADR = adverse drug reaction; 5-FU = 5-fluorouracil; CCI score = Charlson Comorbidity Index score; OR = odds ratio.
*$p < 0.05$.

Table 5

Conditional logistic regression on the risk of hematologic ADR-related with/without hypertension

Variables	Cases (n = 64)	Controls (n = 256)	Crude OR (95% CI)	p	Adjusted OR[a] (95% CI)	p
Without hypertension	30 (46.9%)	186 (72.7%)	Reference		Reference	
Hypertension						
Untreated	11 (17.2%)	19 (7.4%)	3.6 (1.6-8.3)	0.003*	5.3 (1.6-7.5)	0.006*
CCB users	17 (26.6%)	39 (15.2%)	2.7 (1.4-5.3)	0.005*	6.8 (2.4-19.1)	<0.001*
Non-CCB[b] users	6 (9.4%)	12 (4.7%)	3.1 (1.1-8.9)	0.035*	6.9 (1.4-34.8)	0.017*

ADR = adverse drug reaction; CCB = calcium channel blocker; OR = odds ratio.

[a]Adjusted for matching variables (i.e., age and gender), history of hematologic ADR, route of admission, and type of cancer.

[b]Non-CCB includes angiotensin receptor blockers, beta blockers, angiotensin-converting enzyme inhibitors, carvedilol, and diuretics.

*$p < 0.05$.

for hematologic ADRs, as compared with those scored 4 to 6 (OR = 0.22, $p = 0.013$).

To better understand the role of hypertension in chemotherapy-related hematologic ADRs, we further performed subgroup analyses by dividing patients with hypertension into three groups, namely calcium channel blocker (CCB) users, other antihypertensive drug users, and patients with untreated hypertension (Table 5). Compared with patients without hypertension, patients with hypertension who received CCBs or non-CCBs were associated with a higher odds of developing hematologic ADRs (adjusted OR = 6.8 for CCB users, $p < 0.001$; adjusted OR = 6.9 for non-CCB users, $p = 0.019$). Patients with untreated hypertension also had a higher risk of hematologic ADRs than patients without hypertension (adjusted OR = 5.3, $p = 0.005$)

4. DISCUSSION

Our preliminary study found that patients with history of hematologic ADRs (i.e., neutropenia, leucopenia, and pancytopenia), hypertension, CCI score 2 to 3, or under combination chemotherapy with cisplatin but without 5-FU treatment were more likely to be admitted due to neutropenia, leucopenia, or pancytopenia. Notably, the length of hospitalization in our study group (11 days) was similar to the findings of previous studies.[5,6] Moreover, the finding of 93% patients in our study group with a prior episode of neutropenia, leucopenia, or pancytopenia, much higher than in the control (21.9%) indicated that patients with history of hematologic ADRs ran a higher risk of developing recurrent hematologic ADRs. Therefore, physicians and clinical pharmacists should cautiously prescribe chemotherapy drugs to such patients.

Previous studies have indicated that the use of prophylactic G-CSF may help reduce the risk of infection or death from chemotherapy-induced neutropenia.[7–9] Cancer type has also been suggested to be one of the main risk factors in inducing neutropenia, leucopenia, or pancytopenia. However, our study did not find such association between hematologic ADRs and cancer type, possibly because of our relatively small sample size.

Another risk factor, hypertension, was more commonly seen among our patients who had a history of hematologic ADRs. Hypertension is known to be correlated with certain cardiovascular diseases, diabetes, and/or renal diseases; thus, it may potentially affect both the pharmacokinetic mechanisms and pharmacodynamic effects of chemotherapy drugs. For example, we found that the median estimated glomerular filtration rate (eGFR) for hematologic ADR cases who had hypertension was 75.82 mL/min/1.73 m2 in this study, which was significantly lower than those cases without hypertension (median eGFR = 95.36 mL/min/1.73 m2; $p = 0.005$). Moreover, the median eGFR for control patients with hypertension was 79.76 mL/min/1.73 m^2, which was also lower, albeit statistically insignificant, than that in those controls without hypertension (median eGFR = 88.40 mL/min/1.73 m^2).

Another possible explanation for the observed association between hypertension and the risk of hospitalization due to hematologic ADRs is that high blood pressure might be one of the side effects of chemotherapy drugs or other medications (such as those medicines for treating comorbidities). Previous studies have suggested that the administration of captopril and other angiotensin-converting enzyme inhibitors might lead to hematological toxicity such as neutropenia.[10,11] Moreover, cancer patients are at a relatively higher risk of potential drug-drug interactions because many elderly cancer patients may receive multiple medications including chemotherapy drugs and various treatments for comorbidities such as hypertension, diabetes, cardiovascular diseases, and gastrointestinal diseases.[12] A Canadian study has indicated that non-anticancer drugs such as antihypertensive agents, aspirin, warfarin, and anticonvulsants account for 87% of potential drug-drug interactions in cancer patients. Hydrochlorothiazide also can interact with anticancer drugs to prolong neutropenia.[13]

In this study, we further found that hypertensive cases receiving either CCBs or non-CCBs had a higher risk of developing hematologic ADRs than those without antihypertensive drugs (Table 5). We speculate that such a difference may at least be partially attributable to potential drug-drug interactions and/or side effects of anti-hypertensive drugs. Among cases with hypertension, 26.6% of them received CCB treatment, with amlodipine being the most commonly prescribed CCB, followed by diltiazem. To our knowledge, both amlodipine and diltiazem are metabolized via the hepatic cytochrome P450 (CYP) system (mainly 3A4 isoenzyme) and can inhibit the activity of CYP3A4 isoenzyme.[14,15] Coadministration of amlodipine/diltiazem with any other drugs metabolized via the same route may affect the bioavailability of the other drugs. It is noteworthy that several cytotoxic drugs widely used for cancer treatment, such as docetaxel, paclitaxel, etoposide, and irinotecan, are metabolized via CYP3A4.[16–18] Therefore, potential drug-drug interaction between CCBs and chemotherapy drugs may aggravate hematologic ADRs due to increased serum concentrations of cytotoxic drugs via the inhibition of CYP3A4 activity by CCBs. Moreover, we found that the median eGFR of hypertensive cases who received non-CCB treatment (55.84 mL/min/1.73 m2) was much lower than the other cases in this study. We proposed that low renal blood flow among non–CCB-treated hypertensive cases might increase the risk of hematologic ADRs by affecting the excretion of chemotherapy drugs from the kidney.

Compared with all the other types of combination treatment, the combination treatment with cisplatin but without 5-FU had a higher risk of being hospitalized due to hematologic ADRs. A study in Switzerland has indicated that neutropenia (81%), anemia (32%), and thrombocytopenia (4%) constitute the main

toxicities of combination treatment with docetaxel and cisplatin.[14] Other studies have also indicated that cisplatin alone or in combination with other drugs (e.g., pemetrexed/cisplatin, docetaxel/cisplatin, and cisplatin/gemcitabine) is more likely to induce neutropenia and thrombocytopenia, especially in patients with high-dose intensity.[19,20] Another systemic review has observed a possible sequence-dependent relationship between cisplatin and taxanes (e.g., paclitaxel and docetaxel), seeing from their phase I study the decreased clearance of paclitaxel when given after cisplatin. Patients would suffer from more severe neutropenia in this sequence rather than in the opposite sequence.[12] Although our findings were consistent with previous studies, we still thought it is important and worthwhile to thoroughly investigate the role of other chemotherapy drugs concomitantly used with cisplatin, such as cisplatin, ifosfamide, etoposide, gemcitabine, doxorubicin, pemetrexed, paclitaxel, topotecan, vincristine, vinblastine, emthexate, pharmorubicin, bleomycin, and mitomycin-C. Unfortunately, we were unable to determine the association between so many individualized combinations of chemotherapy drugs and the risk of hematologic ADR-related hospitalization from the relatively small sample size of this study. It should be warranted to conduct multi-institutional or population-based studies in the future, by the use of, for example, the Taiwan National Health Insurance Research database.

It was unclear why CCI scores 2 to 3 yielded a higher risk of ADR-related hospitalization than CCI scores 4 to 6, but a lower risk than those scored ≥7. It is possible that physicians would pay more attention to patients who had several comorbidities or were in more severe conditions, thus to reduce the frequency of hospitalizations due to hematologic ADRs in patients scored higher CCI.

In addition to the above-mentioned risk factors for hematologic ADRs, a previous systemic review has also concluded that non–Hodgkin lymphomas (NHLs), lack of G-CSF use, low lymphocyte counts, and chemotherapy dose intensity are also associated with the risk of neutropenia.[9] However, due to the small sample size, our study did not find any significant association of cancer type and low lymphocyte with that risk. The role of chemotherapy dose intensity was not evaluated either, as we did not collect the relevant data.

Taipei Veterans General Hospital as one of the largest medical centers in Taiwan attends to a large proportion of cancer patients (accounting for 38% of all hospitalized patients) and is equipped with fully integrated database to combine inpatient, outpatient, pharmacy, laboratory, and electronic medical records so that patient data collected can be as accurate and complete as possible on their medical charts.

Despite the aforementioned strengths, this study does have some limitations. First, all data were collected retrospectively and we were unable to interview the patients to analyze the detailed circumstances associated with each hematologic ADR event. If data recorded in medical charts were incorrect or incomplete, the findings of this study would be affected accordingly. For example, complete information on medicine use may not be available if a patient received treatment from another hospital as well. Nevertheless, the likelihood was insignificant given that the majority of cancer patients in this study were under regular treatment and outpatient follow-up at Taipei Veterans General Hospital.

Second, although we used ICD-9-CM codes to identify the study patients, the coding of hematologic ADRs might vary among different physicians. To minimize the bias, we had to review all the medical charts as carefully as possible. Furthermore, we reviewed a proportion of patients who were not coded with ICD-9-CM 288.0. As we did not find any coding error associated with hematologic ADRs, we can humbly conclude that diagnostic bias should be minimal.

Third, this is a 1-year study conducted in a single institution; hence, the sample size is relatively small. As such, we do not have adequate statistical power to detect some potentially important determinants of hematologic ADRs and to apply our findings to patients in other institutions. Multi-institutional studies or studies involving a larger research database are warranted in the future for more factors to be identified as the true predictors of hematologic ADRs following chemotherapy that may not exhibit statistical significance in this study.

Fourth, we do not have data on the concentrations of various chemotherapy drugs. Therefore, we are unable to evaluate the magnitude of potential drug-drug interaction between CCBs and chemotherapy drugs that may explain the observed association between hypertension and hematologic ADRs.

Finally, we did not have data on certain confounders such as nutritional status, which could lead to unmeasured confounding effects. The possible difference in the disease duration between the study patients and control subjects might also bias the ORs observed in this case-control study, which included both prevalent and incident cases.

In conclusion, we expect that the predictors of hematologic ADRs observed in this study, such as history of hematologic ADRs, hypertension, CCI score 2 to 3, and combination treatment with cisplatin but without 5-FU, will be useful for healthcare professionals to provide better care for cancer patients. Moreover, precautionary procedures (e.g., prophylactic G-CSF therapy) should be taken to reduce the incidence of hematologic ADRs, the associated medical cost and in-hospital mortality among cancer patients. We also propose that further large-scale studies be conducted to better understand the true risk factors of hematologic ADRs related to chemotherapy and provide more insights into possible preventive strategies.

ACKNOWLEDGMENTS

This study was partly supported by a grant from Taipei Veterans General Hospital (Grant number: V109C-021) and grants from the Ministry of Science & Technology (Grant numbers: MOST 105-2314-B-010-021 and MOST 108-2314-B-010-039), Taipei, Taiwan, ROC.

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