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Chemotherapy-induced thrombocytopenia and clinical bleeding in patients with gynecologic malignancy

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Summary

Objectives: Chemotherapy-induced thrombocytopenia seems to be a relevant problem and the risk of clinical bleeding in patients with gynecologic malignancy is reported to be higher than other malignancy. In this study, the authors investigated chemotherapy-induced thrombocytopenia recently performed in all patients with gynecologic malignancy. *Materials and Methods:* Between January 2009 and December 2011, the authors examined reported chemotherapy-induced thrombocytopenia using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. They analyzed the incidence and clinical features of chemotherapy-induced thrombocytopenia in patients with gynecologic malignancy. *Results:* During this period they administered over 1,614 infusions (29 regimens) to 291 patients. Chemotherapy-induced thrombocytopenia occurred in 43 (14.8%) patients over 56 (3.5%) chemotherapy cycles. Bleeding occurred in 13 (4.5%) patients over 14 (0.9%) cycles. Platelet transfusions were administered for eight (2.7%) patients over eight (0.5%) cycles. Median platelet count at platelet transfusions was 17,000 /μl. Chemotherapy-induced thrombocytopenia was associated with more than five previous chemotherapy cycles, previous radiotherapy, disseminated disease, distant metastatic disease, poor performance status, and taxane-including regimens. Clinical bleeding was associated with previous radiotherapy, distant metastatic disease, poor performance status, and taxane-including regimens. *Conclusions:* Estimating bleeding risk factor such as previous radiotherapy, distant metastatic disease, poor performance status, and taxane-including regimens seem to be important for safe management of chemotherapy-induced thrombocytopenia.

Key words: Chemotherapy-induced thrombocytopenia; Clinical bleeding; Gynecologic malignancy.

Introduction

Patients with gynecologic malignancy often receive several kinds of systemic chemotherapy throughout primary therapy and recurrent therapy. Moreover, new drugs (pegylated liposomal doxorubicin, gemcitabine, etc) were to be used recently in gynecologic malignancy [1, 2].

American Society of Clinical Oncology (ASCO) guideline concluded that the clinical benefit of prophylactic transfusion was at a threshold of 10,000 /μl platelets or less [3]. Gary *et al.* concluded that routine prophylactic platelet transfusion was unnecessary in patients with counts >10,000 /μl [4]. There are many reports investigating chemotherapy-induced thrombocytopenia since first report in 1962, but most reports were studied in patients with leukemia or aplastic anemia [5-7]. The risk of clinical bleeding in patients with gynecologic malignancy reported to be higher than other malignancy [6]. Elting *et al.* concluded that genitourinary and gynecologic neoplasm was one of bleeding risk index [7]. To the present authors' knowledge, the last comprehensive study of thrombocytopenia in patients with gynecologic malignancy was published in 1994 [4]. There are insufficient data from patients who have received modern chemotherapy regimens to address these issues.

In this study, the authors investigated chemotherapy-induced thrombocytopenia recently performed in all patients with gynecologic malignancy with no exception.

Materials and Methods

This retrospective study was approved by Osaka City University, Graduate school of Medicine Institutional Review Board. Using the available electronic medical record data between January 2009 and December 2011, the authors examined their reported chemotherapy-induced thrombocytopenia using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. Complete blood cell counts, including platelet counts were performed on all patients at least once a week. They analyzed the incidence and clinical features of chemotherapy-induced thrombocytopenia (grade 3-4: platelet count <50,000 /μl) in patients with gynecologic malignancy. Episodes of bleeding were categorized as either no bleeding, minor bleeding or major bleeding. Major bleeding was defined as gastrointestinal bleeding, gross hematuria, genital bleeding or intracranial bleeding. Minor bleeding was defined as petechiae, epistaxis, gingival bleeding or blood-tinged sputum. Performance status was measured on day 1 of each cycle using the Eastern Cooperative Oncology Group (ECOG) score. Performance status 3-4 was considered as a poor performance status. Disease sites were categorized as no evidence of disease, local disease, distant metastatic disease, disseminated disease, and both distant metastatic and disseminated disease. Computed tomography (CT) examination

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Table 1. — *Number of patients with gynecologic malignancy.*

Gynecologic malignancy	No. of patients	No. of thrombocytopenia	% of thrombocytopenia	No. of bleeding	% of bleeding
Ovarian cancer	111	17	15	2	2
Endometrial cancer	75	9	12	2	3
Cervical cancer	73	13	18	7	10
Peritoneal cancer	14	2	14	0	0
Uterine carcinosarcoma	5	0	0	0	0
Vaginal cancer	4	1	25	1	25
Choriocarcinoma	2	1	50	1	50
Uterine sarcoma	2	0	0	0	0
Clinical invasive mole	1	0	0	0	0
Endometrial stromal sarcoma	1	0	0	0	0
Vaginal melanoma	1	0	0	0	0
Bartholin gland carcinoma	1	1	100	0	0
Ovarian & endometrial cancer (double)	1	0	0	0	0

Thrombocytopenia: chemotherapy-induced thrombocytopenia (CTCAE v.4.0: grade 3-4).

Table 2. — *Regimen of chemotherapy performed between January 2009 and December 2011.*

Regimen	No. of courses	No. of patients	No. of thrombocytopenia	% of thrombocytopenia	No. of bleeding	% of bleeding
TC (PTX+CBDCA)	677	152	21	3	1	0
DC (DTX+CBDCA)	176	40	1	1	0	0
weekly CDDP	124	25	0	0	0	0
CPT-11+CDDP	119	31	5	4	0	0
CDGP	91	26	6	7	4	4
PLD	86	22	3	3	0	0
CDDP	50	14	1	2	1	2
CPT-11+CDGP	43	16	6	14	2	5
CPT-11	42	18	2	5	1	2
DTX+CDGP	31	6	0	0	0	0
PTX	31	6	0	0	0	0
AP (ADR+CDDP)	27	8	2	7	1	4
THP-ADR+CDDP	22	4	0	0	0	0
EMA/CO (VP-16+MTX+ACD+CPA+VCR)	16	2	5	31	2	13
CDDP+S-1	10	1	0	0	0	0
DTX	10	1	0	0	0	0
GEM	9	4	0	0	0	0
CPT-11+PTX	8	1	0	0	0	0
EP/MEA (VP-16+CDDP+MTX+ACD)	8	1	0	0	0	0
ADR	5	2	0	0	0	0
CPT-11+MMC	5	3	2	40	0	0
DAVFeron (DTIC+ACNU+VCR+IFN-beta)	5	1	0	0	0	0
MTX	5	1	0	0	0	0
BEP (BLM+VP-16+CDDP)	3	1	0	0	0	0
weekly CDGP	3	1	0	0	0	0
DTX+GEM	3	2	0	0	0	0
CAP (CPA+ADR+CDDP)	2	1	1	50	1	50
CPT-11+VP-16	2	1	0	0	0	0
TP (PTX+CDDP)	1	1	1	100	1	100

PTX: paclitaxel; CBDCA: carboplatin; DTX: docetaxel; CDDP: cisplatin; CDGP: nedaplatin; CPT-11: irinotecan; PLD: pegylated liposomal doxorubicin; ADR: adriamycin; THP-ADR: tetrahydropyranyladriamycin; VP-16: etoposide; MTX: methotrexate; ACD: actinomycin D; CPA: cyclophosphamide; VCR: vincristine; GEM: gemcitabine; MMC: mitomycin C; DTIC: dacarbazine; ACNU: nitrosourea; IFN-beta: interferon-beta; BLM: bleomycin.

of the abdomen and chest or magnetic resonance imaging (MRI) examination of pelvis was performed on all patients at least once per 3 chemotherapy cycles. Disease sites and bone marrow metastasis were evaluated such a variety of imaging examination including positron emission tomography (PET). Febrile neutropenia was defined as an oral temperature >38.3°C or two consecutive readings of >38.0°C for two hours and an absolute neutrophil count < 0.5×10^9/l, or expected to fall below 0.5×10^9/l.

Statistical analysis

The relationship between each clinical group was analyzed using the Fisher's exact probability test. A p value of less than 0.05 was considered significant.

Table 3. — *Risk of chemotherapy-induced thrombocytopenia and clinical bleeding related clinical characteristics.*

		No. of courses	No. of thrombocytopenia	% of thrombocytopenia	No. of bleeding	% of bleeding
Age	< 70 years	1283	49	3.8	12	0.9
	≥ 70 years	331	7	2.1	2	0.6
Performance status	0-2	1544	42	2.7	11	0.7
	3-4	70	14	20.0	3	4.3
Disease	No evidence of disease	391	5	1.3	1	0.3
	Local disease	253	6	2.4	3	1.2
	Distant metastatic disease	216	8	3.7	2	0.9
	Disseminated disease	414	17	4.1	1	0.2
	Metastatic and disseminated disease	340	20	5.9	7	2.1
Bone marrow metastasis	Yes	72	4	5.6	2	2.8
	No	1542	52	3.4	12	0.8
Prior cycle	None	196	4	2.0	2	1.0
	1-5 cycles	775	21	2.7	9	1.2
	6-10 cycles	301	17	5.6	0	0
	>10 cycles	342	14	4.1	3	0.9
Prior radiotherapy	Yes	73	11	15.1	4	5.5
	No	1541	45	2.9	10	0.6
Regimen	Monotherapy	456	12	2.6	6	1.3
	Combined therapy	1158	44	3.8	8	0.7
Platinum-based regimen	Yes	1387	44	3.2	11	0.8
	No	227	12	5.3	3	1.3
Taxane-including regimen	Yes	937	23	2.5	2	0.2
	No	677	33	4.9	12	1.8

Thrombocytopenia: chemotherapy-induced thrombocytopenia (CTCAE v.4.0: grade3-4)

Table 4. — *Patients with platelet transfusion.*

Patient No.	Age	Disease	Regimen	Platelet count (/μl)	Bleeding episode	Febrile neutropenia	No. of units transfused
1	64	ovarian cancer	DC (DTX+CBDCA)	15,000	(-)	(+)	30
2	36	cervical cancer	CPT-11+CDGP	6,000	gastrointestinal bleeding	(+)	40
3	43	ovarian cancer	TC (PTX+CBDCA)	17,000	(-)	(+)	20
4	59	endometrial cancer	TC (PTX+CBDCA)	28,000	gastrointestinal bleeding	(+)	25
5	62	cervical cancer	CDGP	11,000	gingival bleeding	(-)	10
6	55	peritoneal cancer	TC (PTX+CBDCA)	29,000	(-)	(+)	10
7	68	ovarian cancer	TC (PTX+CBDCA)	22,000	(-)	(+)	25
8	52	endometrial cancer	AP (ADR+CDDP)	17,000	gastrointestinal bleeding	(-)	10

DTX: docetaxel; CBDCA: carboplatin; CPT-11: irinotecan; CDGP: nedaplatin; PTX: paclitaxel; ADR: adriamycin; CDDP: cisplatin.

Results

Incidence of chemotherapy-induced thrombocytopenia and clinical bleeding

The patients with gynecologic malignancy and chemotherapy regimens are shown in Tables 1 and 2. During this period the authors administered over 1,614 infusions (29 regimens) to 291 patients with gynecologic malignancy. Median age was 60 years (24-84). The most common gynecologic malignancies were ovarian cancer (111 patients: 38%), endometrial cancer (75 patients: 26%, and cervical cancer (73 patients: 25%). All patients had received conventional cytotoxic chemotherapy. There was no use of targeted treatment, such as monoclonal antibodies or tyrosine kinase inhibitors. The most common chemotherapy regimen was TC (paclitaxel and carboplatin) therapy; 152 patients (52%) received 677 courses (42%) of TC therapy in total. Chemotherapy-induced thrombocytopenia occurred in 43 (14.8%) patients over 56 (3.5%) chemotherapy cycles. Clinical bleeding occurred in 13 (4.5%) patients over 14 (0.9%) cycles. Major bleeding occurred in seven (2.4%) over seven (0.4%) cycles (gastrointestinal bleeding: four, genital bleeding: two, gross hematuria: one). In other seven cycles, clinical bleeding were minor bleeding (petechiae: four, epistaxis: one, gingival bleeding: one, blood-tinged sputum: one). No life-threatening bleeding occurred in any patient.

Clinical features of chemotherapy-induced thrombocytopenia and clinical bleeding

Risk of chemotherapy-induced thrombocytopenia and clinical bleeding related clinical characteristics are shown in Table 3. Chemotherapy-induced thrombocytopenia was associated with more than five previous chemotherapy cycles

($p = 0.03$), previous radiotherapy ($p = 0.0001$), disseminated disease ($p = 0.006$), distant metastatic disease ($p = 0.02$), and poor performance status ($p = 0.0001$). Chemotherapy-induced thrombocytopenia was not related with age or bone marrow metastases. Clinical bleeding was associated with previous radiotherapy ($p = 0.003$), distant metastatic disease ($p = 0.03$), and poor performance status ($p = 0.02$). Clinical bleeding was not related with more than five previous chemotherapy cycles, disseminated disease, age or bone marrow metastases.

Both chemotherapy-induced thrombocytopenia and clinical bleeding were not related with platinum-based regimens or number of anti-cancer drug of regimens. Taxane-including regimens were associated with lower rate of thrombocytopenia ($p = 0.01$) and clinical bleeding ($p = 0.002$).

Febrile neutropenia was complicated with 19 (35%) of thrombocytopenia cycles and six (43%) of clinical bleeding cycles. Infection was complicated with 29 (52%) of thrombocytopenia cycles and nine (64%) of clinical bleeding cycles.

Platelet transfusion

The patients with platelet transfusion are shown in Table 4. Platelet transfusions were administered for eight (2.7%) patients over eight (0.5%) cycles. Clinical bleeding was observed in four cycles and febrile neutropenia was observed in six cycles. In four cycles with clinical bleeding, platelet transfusions were administered after their bleeding episode and clinical bleeding stopped in a few days. In four cycles without clinical bleeding, platelet transfusions were administered before their bleeding episode began. Median platelet count at platelet transfusions was 17,000 /μl (6,000 - 29,000). Median number of platelet units for each cycle was 25 units (10-40). Platelet transfusion reactions were not observed in any patient.

Discussion

The patients with gynecologic malignancy often received systemic chemotherapy as one of primary therapy. Moreover, most patients with recurrent disease received chemotherapy. As a result, patients with gynecologic malignancy received several kinds of chemotherapy and received frequent chemotherapy per patient in clinical practice.

On the other hand, it is to be assumed that chemotherapy-induced thrombocytopenia seemed to be more problematic in the safe management of chemotherapy as the outpatient chemotherapy is performed more frequently. Chemotherapy-induced thrombocytopenia is a known source of great stress to physicians and patients. Major bleeding during chemotherapy-induced thrombocytopenia is a serious clinical problem. In some cases, platelets are administered to patients with malignancy for preventing such events. The risk of clinical bleeding in patients with gynecologic malignancy reported to be higher than other malignancies [6, 7].

There were many reports investigating chemotherapy-induced thrombocytopenia. Several clinical trials have demonstrated the potential for a 10,000 platelet /μl threshold in patients with acute leukemia [8-10]. Although there were many reports investigating chemotherapy-induced thrombocytopenia, most reports were studied in patients with leukemia or aplastic anemia [5-7]. Although there were some reports investigating chemotherapy-induced thrombocytopenia in patients with solid tumors, only a small number of patients with gynecologic malignancy were included [6, 7]. To the present authors' knowledge, the last comprehensive study of thrombocytopenia in patients with gynecologic malignancy was published by Gary *et al.* in 1994 [4]. They concluded that routine prophylactic platelet transfusion was unnecessary in patients with counts >10,000 /μl [4]. In their study, taxane was not yet used and chemoradiotherapy was not performed frequently in patients with cervical cancer. There are insufficient data from patients who have received modern chemotherapy regimens to address these issues. Primary purpose of this study was to clarify risk factor of clinical bleeding during chemotherapy-induced thrombocytopenia.

In the present study, chemotherapy-induced thrombocytopenia was defined as platelet count <50,000 /μl (grade 3-4) using the CTCAE v.4.0. In previous reports, chemotherapy-induced thrombocytopenia was defined as platelet count <50,000 /μl, <75,000 /μl or <100,000 /μl [4, 6, 7, 11]. In clinical practice, there are only a few cases of severe bleeding and platelet transfusions in patients with platelet count >50,000 /μl. For this reason, the present authors' definition of chemotherapy-induced thrombocytopenia was reasonable.

In this study, chemotherapy-induced thrombocytopenia occurred in 14.8% of patients over 3.5% of chemotherapy cycles. Gary *et al.* reported that chemotherapy-induced thrombocytopenia (platelet count <100,000 /μl) occurred in 36.3% of patients with gynecologic malignancy and over 52% of cycles with these patients resulted in thrombocytopenia [4]. Hitron *et al.* reported that chemotherapy-induced thrombocytopenia (platelet count <75,000 /μl) occurred in 10.1% of patients with solid tumors [11]. The present findings were similar to previous reports.

On the other hand, clinical bleeding occurred in 4.5% of patients over 0.9% of cycles in the present study. Major bleeding occurred in 2.4% patients over 0.4% of cycles (gastrointestinal bleeding, genital bleeding, and gross hematuria). Gary *et al.* reported that clinical bleeding was in 23.6% of patients and over 6.7% of cycles in patients with chemotherapy-induced thrombocytopenia (platelet count <100,000 /μ.) with gynecologic malignancy. In their report, major bleeding was in 4.9% of patients and over

1.3% of cycles in patients with thrombocytopenia [4]. Elting *et al.* reported that clinical bleeding was in 9% of cycles and major bleeding was in 3% of cycles in patients with chemotherapy-induced thrombocytopenia (platelet count <50,000 /μl) with solid tumors [6]. The present data showed lower rate of clinical bleeding than these reports. These reports were investigated before 1995 and taxanes were not used. Moreover new drugs (pegylated liposomal doxorubicin, gemcitabine, etc) were to be used recently in gynecologic malignancy [1, 2]. Major change in chemotherapy regimens seemed to affect lower rate of clinical bleeding with patients in gynecologic malignancy. In this study, no life-threatening bleeding occurred in any patient. Gary *et al.* reported that no intracranial bleeding or other serous clinical effects from hemorrhage were observed in their study [4]. The present data was similar to their report.

Furthermore, the present authors investigated risk of thrombocytopenia and clinical bleeding related clinical characteristics. Especially, disease sites were categorized as no evidence of disease, local disease, distant metastatic disease, disseminated disease, and both distant metastatic and disseminated disease in this study. In Elting's reports, disease sites were categorized as no evidence of disease, local disease, one metastatic disease, disseminated disease [6]. Chemotherapy-induced thrombocytopenia was associated with more than five previous chemotherapy cycles, previous radiotherapy, disseminated disease, distant metastatic disease, and poor performance status. Clinical bleeding was associated with previous radiotherapy, distant metastatic disease, and poor performance status. Both chemotherapy-induced thrombocytopenia and clinical bleeding were not related with age, bone marrow metastases or platinum-based regimens. Elting *et al.* reported that bleeding was associated with previous bleeding episodes, baseline platelet count less than 75,000 /μl, disseminated disease, poor performance status, bone marrow metastases, and cisplatin, carboplatin, carmustine or lomustine administration [6]. Most clinical bleeding before primary therapy was from uterine in patients with gynecologic malignancy and hysterectomy was performed in most cases. Therefore, the present authors did not consider previous bleeding episodes as a risk factor related with chemotherapy-induced thrombocytopenia and clinical bleeding. This study included no cycles with baseline platelet count less than 75,000 /μl because the authors performed chemotherapy on patients with baseline platelet count more than 75,000 /μl. In their report, disseminated disease was defined as one or more site of metastasis. The present results combined with their report confirm that bleeding is associated with metastatic disease and poor performance status. Although clinical bleeding was not related with bone marrow metastases, clinical bleeding was associated with previous radiotherapy. The present results combined with their report confirm that bleeding is associated with poor bone marrow reserve. This data also suggested that chemotherapy-induced thrombocytopenia was associated with poor bone marrow reserve (five previous chemotherapy cycles and previous radiotherapy) and poor general condition (disseminated disease, distant metastatic disease, and poor performance status). In this study, both chemotherapy-induced thrombocytopenia and clinical bleeding were not related with platinum-based regimens. Taxane-including regimens were associated with lower rate of thrombocytopenia ($p = 0.01$) and clinical bleeding ($p = 0.002$). Elting *et al.* reported that bleeding was associated with cisplatin, carboplatin, carmustine or lomustine administration [6]. Although most of platinum-based regimens did not include taxane in their report, more than 60% of platinum-based regimens included taxane in the present study. This seemed to be a reason for no relationship between thrombocytopenia and platinum-based regimens. To the present authors' knowledge, there was no comprehensive study investigating a relationship between taxane-including regimens and chemotherapy-induced thrombocytopenia in patients with gynecologic malignancy. Despite more than 90% of taxane-including regimens included platinum drug in the present study, taxane-including regimens were associated with lower rate of chemotherapy-induced thrombocytopenia and clinical bleeding. This seemed to be necessary for taking into consideration of using taxane-including regimens in high risk cases of bleeding.

Platelet transfusions were administered in eight (2.7%) patients over eight (0.5%) cycles in this study. Median platelet count at platelet transfusions was 17,000 /μl (6,000-29,000). ASCO guidelines [3] concluded the risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth of the platelet nadir, although other factors contribute as well. Evidence obtained from observational studies supports the clinical benefit of prophylactic transfusion at a threshold of 10,000 /μl platelets or less. The Panel suggests, however, on the basis of expert clinical opinion, that prophylactic transfusion at a threshold of 20,000 /μl be considered for patients receiving aggressive therapy for bladder tumors, as well as those with demonstrated necrotic tumors, owing to their presumed increased risk of bleeding at these sites. Platelet transfusions were administered in the present hospital according to ASCO guideline. In this study, clinical bleeding was observed in four cycles and febrile neutropenia was observed in six cycles. In any cases with platelet transfusion, at least one of these states was filled as followed; platelet count <10,000 /μl, bleeding episode or febrile neutropenia. In four cycles with clinical bleeding, platelet transfusions were administered after their bleeding episode and clinical bleeding stopped in a few days. In four cycles without clinical bleeding, platelet transfu-

sions were administered before their bleeding episode began. Platelet transfusions may appear to be any benefit in the prevention of the subsequent bleeding.

In conclusion, chemotherapy-induced thrombocytopenia and clinical bleeding are not so frequent in patients with gynecologic malignancy. Estimating risk factor of clinical bleeding such as previous radiotherapy, distant metastatic disease, and poor performance status seemed to be important for safe management of chemotherapy-induced thrombocytopenia without unnecessary platelet transfusion.

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