Vinorelbine plus 24-Hour Infusion of High-dose 5-Fluorouracil and Leucovorin as Effective Palliative Chemotherapy for Breast Cancer Patients with Acute Disseminated Intravascular Coagulation

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Abstract. *Background: Cancer-related acute disseminated intravascular coagulation (DIC) is uncommon, but it is a severe complication resulting in a very dismal prognosis. Choosing the appropriate chemotherapy agents to treat the underlying cancer and stop the acute DIC process effectively, while avoiding chemotherapy-induced myelosuppression which may contribute to bleeding-related mortality, is difficult. Acute DIC in breast cancer is a rare condition and is not well studied. Therefore, we designed this study to determine the clinical characteristics and effective treatment for breast cancer patients with acute DIC. Patients and Methods: From March 1996 to November 2008, patients with histologically proven breast cancer who presented with acute DIC at National Taiwan University Hospital were retrospectively analyzed. Results: Sixteen patients were included in the study. Thirteen patients with breast cancer-related acute DIC were treated with various kinds of chemotherapy, one with tamoxifen, and two with supportive care only. Four patients responded to treatment; three of the responders received vinorelbine with high-dose 5-fluorouracil and leucovorin (HDFL), the other received vinorelbine with cisplatin. The median survival of the responders and non-responders was 13 months and 0.5 month (p<0.001). There were no grade 3 or 4 hematologic or non-hematologic toxicities in the patients receiving vinorelbine-HDFL. Conclusion: Vinorelbine plus HDFL is considered a safe and effective palliative treatment of choice for breast cancer patients with acute DIC. Further prospective study is warranted.*

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The association between cancer and abnormal hemostasis was first described by Armand Trousseau in 1865 (1) and has been well known to clinicians since then. The manifestations of cancer-related hemostatic perburbation are variable (2, 3). In most instances, cancer patients develop a venous thromboembolism, such as deep vein thrombosis or pulmonary embolism. In others, the pretubation may occur as consumptive coagulopathy, or as an acute disseminated intravascular coagulation (DIC) with hemorrhagic manifestations. The mortality rate of cancer-related acute DIC is extremely high because of severe thrombocytopenia, organ dysfunction and bleeding complications (4, 5). Aside from supportive care, effective chemotherapy against the underlying cancer plays the only key role to control the acute DIC. However, choosing an appropriate and effective chemotherapy regimen in this critical condition is very difficult because of the damage of chemotherapy-induced myelosuppression, which may enhance the severe thrombocytopenia and contribute to bleeding-related mortality.

Breast cancer is one of the most common types of cancer and is a leading cause of cancer-related death in women throughout the world (6). Abnormal coagulation status is occasionally found in patients with breast cancer, with the most common manifestation being venous thromboembolism without bleeding tendency (7). However, breast cancer-related acute DIC is a rare and not well-studied condition (8). In this retrospective study, we investigated the clinical characteristics and treatment outcome of breast cancer patients with acute DIC among overall patients during 1996 and 2008 at our institution.

Patients and Methods

Patients. Between March 1996 to November 2008, patients with histologically proven breast cancer who presented with acute DIC at The National Taiwan University Hospital were retrospectively analyzed. The diagnosis of acute DIC was based on the following criteria: evidence of bleeding symptoms/signs with laboratory findings, including progressive thrombocytopenia, prolonged prothrombin time (international normalized ratio ≥1.3) or activated partial thromboplastin time, decreased serum fibrinogen levels and elevated D-dimer levels.

At diagnosis, all patients underwent blood testing for hemogram, biochemistry panel, and DIC profiles. Other relevant studies, such as computed tomographic scans of the lesion sites, esophagogastroduodenoscopy, bone scan or bone marrow biopsy were performed for patients with specific symptoms. Patient characteristics are shown in Table I.

Treatment. Patients received various treatments based on their condition and attending doctors' decision. The treatments are listed in the Table II.

Definition of response. The response of acute DIC to treatment was evaluated by serial laboratory testing and reduction of clinical bleeding symptoms/signs. Response to treatment was defined as a combination of clinical resolution of bleeding tendency and improvement of laboratory data, such as increased platelet counts and reduced D-dimer level, for a durable duration of at least 4 weeks.

Results

A total of 5,459 patients with histologically proven breast cancer were identified from our comprehensive database of the Department of Medical Records from March 1996 to November 2008; 1,436 patients developed metastatic breast cancer. Using the key phrase "disseminated intravascular coagulation" to search the comprehensive database of patients with breast cancer, 52 patients were identified: 25 patients were recorded as having sepsis-related DIC, 4 patients were without detailed laboratory or clinical records, and 7 patients had only mild positive D-dimer without thrombocytopenia and clinical bleeding tendency. Sixteen patients met the criteria of acute decompensate DIC, and all of them were recognized as having cancer-related acute DIC at that time.

Clinicopathological characteristics (Table I). The 16 patients had metastatic breast cancer, and their median age was 47.5 years (range: 29 to 77 years). Two were newly-diagnosed breast cancer patients, three had recurrent breast cancer (recurrence after mastectomy, adjuvant chemotherapy with or without hormone therapy), and eleven were in a progressive disease status. All of them had infiltrating ductal carcinoma. Nine out of sixteen (56.3%) patients' tumors were negative for estrogen receptor (ER) expression, and three out of seven patients whose tumor underwent Her2 immunohistochemical staining were positive for Her2/neu expression. Eight patients received bone marrow examinations, and six were identified as having bone marrow metastasis. The liver and bone were the most common metastatic sites, followed by lung, bone marrow and others. With the exception of the two newly-diagnosed breast cancer patients, all patients had received a variety of prior chemotherapy agents, included tanxanes and anthracyclines.

Acute DIC was one of the presenting symptom/signs in all patients. Eight patients had mucocutaneous bleeding; eight had gastrointestinal bleeding; four patients had hematuria. All patients had anemia and thrombocytopenia at diagnosis. All of them also had an elevated D-dimer level and prolonged prothrombin time or activated partial thromboplastin time. The DIC profiles of these 16 patients are summarized in Table II.

Treatments and response. All patients received supportive care, such as packed RBC, platelet and fresh frozen plasma transfusion, for the bleeding tendency. Ten patients received weekly 24-hour high-dose 5-fluorouracil (5-FU) and leucovorin (HDFL), or HDFL-containing combination regimens (five with HDFL alone, three combined HDFL with vinorelbine, two combined HDFL with cisplatin). Of the others, one was treated with cisplatin and vinorelbine, one with cisplatin and docetaxel, one with gemcitabine, one with tamoxifen, and two with best supportive care only. Four patients had a response to treatment, and twelve did not. All of the non-responders died very soon after the diagnosis of acute DIC.

Three out of the four responders had received vinorelbine with HDFL, and the other had received vinorelbine with cisplatin. However, five patients that received HDFL alone were non-responders. The vinorelbine-HDFL was administered as follows: vinorelbine 25 mg/m^2 on day 1 and day 8; 5-FU 2600 mg/m^2 plus leucovorin 300 mg/m^2, 24 h infusion on day 1 and day 8, repeated every 21 days (9). After these three patients had undergone one course of vinorelbine-HDFL, the platelet counts were substantially increased, and the D-dimer level effectively decreased. The patients received a median of four courses of vinorelbine-HDFL until disease progression, and subsequently received other chemotherapies to control the breast cancer. The fourth patient was treated with vinorelbine and cisplatin (vinorelbine 20 mg on day 1; cisplatin 27.5 mg on day 2). Her acute DIC also improved, and she received subsequent chemotherapy. Among the four responders, there was no grade 3 or 4 neutropenia. Thrombocytopenia and coagulopathy improved gradually after chemotherapy. No infectious complication was noted during chemotherapy. The non-hematologic toxicities were almost negligible.

Survival. The median overall survival of the non-responders was only 0.5 month, and they were unable to receive any another treatment because of rapid deterioration of their clinical conditions. At the time of this report, two out of the

Table I. *Characteristics of patients*.

	Age (years)	Pathology	ER/PR/ HER2	Metastasis	Disease status	Prior chemotherapy
#1	39	IDC	+/+/-	Bone, bone marrow	New diagnosis	Nil
#2	58	IDC	+/+/NA	Bone	PD	Multiple
#3	57	IDC	-/-/+	Neck LN	PD	Docetaxel, cisplatin, capcitabine
#4	38	IDC	-/-/-	Liver, bone	Recurrence	CEF, docetaxel
#5	65	IDC	-/-/NA	Liver, neck LN	PD	CMF, docetaxel, paclitaxel, HDFL
#6	29	IDC	+/+/+	Liver, lung, bone	PD	CEF, docetaxel, vinorelbine
#7	48	IDC	-/-/-	Liver, lung, bone marrow	PD	Multiple
#8	37	IDC	+/-/NA	Liver, lung, bone, bone marrow, brain,	PD	Multiple
#9	65	IDC	+/+/-	Liver, lung, bone	PD	CEF, docetaxel, vinorelbine
#10	42	IDC	-/+/NA	Liver, bone, neck LN	Recurrence	CEF
#11	48	IDC	+/+/NA	Liver, lung, bone, bone marrow	Recurrence	AC, paclitaxel
#12	47	IDC	-/-/NA	Liver, lung, bone, bone marrow	PD	Paclitaxel, cisplatin
#13	51	IDC	+/+/NA	Liver, bone	PD	CEF, vinorelbine, cisplatin, docetaxel
#14	43	IDC	-/-/NA	Lung, bone, bone marrow	PD	CMF, CEF, HDFL
#15	77	IDC	-/-/+	Liver, bone, skin	New diagnosis	Nil
#16	36	IDC	-/-/NA	Liver	PD	Multiple

IDC: Infiltrating ductal carcinoma; LN: lymph nodes; PD: progressive disease; CEF: cyclophosphamide, epirubicin, and fluorouracil; CMF: cyclophosphamide, methotrexate, and fluorouracil; AC: doxorubicin and cyclophosphamide; ER: estrogen receptor; PR: progesterone receptor; HER2: Her2/neu status.

Table II. *DIC profiles and treatments given for breast cancer patients*.

	Hb (g/dl)	Platelet ($\times10^3$/µl)	PT INR	aPTT (s)	D-dimer	Treatment	Response	Platelet ($\times10^3$/µl)	D-dimer (µg/ml)	Outcome, survival (months)[a]
#1	7.7	43	1.32	34.9	2.39 µg/ml	Vinorelbine + HDFL	Y	112	-	Died, 39
#2	7.8	68	1.3	30.2	7.98 µg/ml	Vinorelbine + HDFL	Y	166	2.11	Alive, 12
#3	8.9	33	1.3	30.4	2.28 µg/ml	Vinorelbine + HDFL	Y	91	1.01	Alive, 13
#4	12.7	6	1.82	>200	1701 ng/ml[b]	Cisplatin+vinorelbine	Y	169	1.82	Died, 11
#5	9.5	32	2.2	57	8.16 µg/ml	Cisplatin+docetaxel	N	-	-	Died, 0.5
#6	8.7	24	1.44	150	48.6 µg/ml	Cisplatin+HDFL	N	-	-	Died, 1
#7	5.4	33	>10	>200	>1:1280[c]	Gemcitabine	N	-	-	Died, 1
#8	8.6	6	2.2	120	4.8 µg/ml	HDFL	N	-	-	Died, 0.5
#9	8.6	9	1.5	86.8	8.8 µg/ml	HDFL	N	-	-	Died, 1
#10	8.1	27	2.2	113.8	17.78 µg/ml	HDFL	N	-	-	Died, 1
#11	7.3	88	3.2	58.5	17.21 µg/ml	Tamoxifen	N	-	-	Died, 0
#12	9.6	27	1.2	44.7	4+[c]	HDFL	N	-	-	Died, 1
#13	9.2	56	1.4	31.2	21.03 µg/ml	HDFL	N	-	-	Died, 0.5
#14	8	71	1.6	53.3	1:320[c]	No treatment	N	-	-	Died, 0
#15	7.7	88	-	-	5.77 µg/ml	Cisplatin+HDFL	N	-	-	Died, 0.5
#16	9.4	123	1.3	54.6	-	No treatment	N	-	-	Died, 0

Hb: Hemoglobin; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time. [a]Survival time was determined from the time patients were diagnosed as having acute DIC. Due to the long period of this retrospective study, methods of D-dimer measurement were different. [b]D-dimer was measured by D-Dimer Plus (Dade Behring Inc.), which is a latex-enhanced turbidmetric test for quantitative determination of D-dimer in human plasma. A D-dimer level >324 ng/ml is considered as a positive result. [c]D-dimer was measured by a semi-quantitative test, which is a rapid latex agglutination slide method using monoclonal antibody for semi-quantitative determination of D-dimer in plasma. The others were measured by Advanced D-Dimer (Dade Behring Inc.), which is a latex-enhanced immunoturbidmetric test for quantitative determination of D-dimer using Dade Behring Coagulation Analyzer and Sysmex® Coagulation Systems. D-dimer >1 µg/ml is considered as a positive result.

four responders were still alive (12 and 24 months after diagnosis of metastasis), and underwent active treatments. No evidence of recurrent acute DIC was noted. The median overall survival of the four patients was 13 months, which was significant longer than that of the 13 non-responders ($p<0.001$).

Discussion

Breast cancer is rarely associated with acute DIC (8). However, cancer-related acute DIC is a critical and lethal clinical condition (5). In this retrospective study, vinorelbine-HDFL and vinorelbine-cisplatin were able to effectively rescue four patients from this dismal condition without chemotherapy-related complications. The four responders had a significantly more favorable prognosis than non-responders.

Cancer-related DIC is usually presents as chronic thromboembolism, and heparin or low-molecular weight heparin is used in this condition (10, 11). However, heparin is ineffective and might be harmful to patients with acute DIC (10, 11). Patients usually die soon after the diagnosis of cancer-related acute DIC because of severe thrombocytopenia, progressive organ dysfunction and uncontrolled bleeding. Stopping the acute DIC process requires adequate control of the underlying malignancy (10, 12). Chemotherapy is beneficial to tumor control, but chemotherapy-related toxicities may enhance the bleeding complication, resulting in mortality. A non-myelosuppressive and effective chemotherapy regimen is considered the only suitable palliative treatment in this critical condition (13).

The effectiveness of vinorelbine-HDFL is reflected in the fact that three out of three patients who received vinorelbine-HDFL had improvement in their acute DIC. One patient who received vinorelbine-cisplatin also had remission of acute DIC. Although the number of patients was limited, these chemotherapy regimens provided a good response, and also a better prognosis than the other treatments given.

In the previous studies, gastric cancer was most commonly associated with acute DIC (13, 14), and it also causes high mortality. We have developed HDFL, a non-myelosuppressive chemotherapy regimen, as a safe and effective treatment for gastric cancer patients with acute DIC (13). We reported that 14 out of 19 patients with acute DIC attained clinical remission of the gastric cancer (15) and suggested that initial HDFL monotherapy can alleviate this critical condition, and enable patients to further receive conventional chemotherapy such as cisplatin plus HDFL. However, in the current study, vinorelbine plus HDFL may serve as an effective therapy in breast cancer patients with acute DIC. In our previous phase II study of combined weekly vinorelbine and HDFL, patients with advanced breast cancer had a high response rate (70%) and well-tolerated toxicities for first-line treatment (9). The possible explanation for the effectiveness of HDFL doublets is that breast cancer has different biologic characteristics from metastatic gastric cancer. Moreover, the mechanism of cancer-related abnormal hemostasis is very complex (3). Different types of cancer may disrupt different thrombotic and anti-thrombotic pathways.

This study is the first of a relatively large patient series to report on this rare breast cancer-related acute DIC entity. Among the clinical characteristics, 9 out of 16 (56.3%) patients had ER-negative breast cancer. Her2/neu status was examined in 7 patients, and 3 of them were found to be positive. ER negativity and Her2/neu positivity are both poor prognostic factors (16, 17), and the incidence of these factors in the 16 patients was higher compared with that of the general population of breast cancer patients (18). Six out of eight patients had bone marrow metastasis of breast cancer, which indicated that patients had disseminated disease. In gastric cancer, nearly 100% of acute DIC patients have bone marrow metastasis (13, 15). This special presentation may be associated with acute DIC. Further research to determine the mechanisms which link bone marrow metastasis and acute DIC may be helpful to treatment.

In conclusion, vinorelbine plus HDFL appears to be a safe and effective treatment for breast cancer patients with acute DIC. Further prospective study is warranted.

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