Weekly 24-hour Infusional 5-Fluorouracil as Initial Treatment for Advanced Gastric Cancer with Acute Disseminated Intravascular Coagulation

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Abstract. *Background: Acute disseminated intravascular coagulation (DIC) occurring in patients with advanced gastric cancer (AGC) is a rare entity with a dismal prognosis. Conventional cytotoxic chemotherapy is usually not possible. Preliminary reports have suggested that non-myelosuppressive weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) and leucovorin (HDFL) may be helpful. Patients and Methods: Between 1994 and 2005, AGC patients who presented with acute DIC and were initially treated with HDFL (5-FU 2600 mg/m^2 plus leucovorin 300 mg/m^2, 24-h infusion weekly) were reviewed. Results: Nineteen such patients were identified. After treatment with HDFL for a median of 4 weeks, 14 patients showed a response of the acute DIC. Eight of them subsequently received HDFL-based combination chemotherapy. The median survivals for the whole group, the DIC responders, and the 8 patients receiving subsequent combination chemotherapy were 3, 6, and 8 months, respectively. Conclusion: HDFL, as a safe initial treatment for AGC patients with acute DIC, provides the opportunity for further aggressive chemotherapy.*

Advanced gastric cancer (AGS) presenting with acute disseminated coagulation (DIC) is a rare disease entity (1). The manifestations of acute DIC may include a tendency to bleeding, infarction and, occasionally, microangiopathic hemolytic anemia (MAHA) or thrombotic thrombocytopenic purpura (2). The outcome for patients with AGS and acute DIC is extremely poor, with a survival time usually no more than 1 month despite active supportive care (3).

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Key Words: Gastric cancer, disseminated intravascular coagulation, bone marrow metastasis, 5-fluorouracil infusional therapy.

The optimal treatment for AGC patients with acute DIC remains unknown. Since active supportive care is generally unsuccessful, effective systemic chemotherapy against the underlying malignancy may be the only way to control the cancer-associated DIC. Chemotherapy combining 5-fluorouracil (5-FU) and other cytotoxic drugs, such as cisplatin, has been widely used in advanced gastric cancer, resulting in high tumor response rates and improved survival (4, 5). Unfortunately, the use of these combination chemotherapy regimens in patients with acute DIC has been limited by inevitable bone marrow toxicity.

Previously, we have shown that weekly 24-h infusion of high-dose 5-FU and leucovorin (*i.e.* the HDFL regimen: 5-FU 2600 mg/m^2 plus leucovorin 300 mg/m^2, 24-h infusion, per week) was an effective and safe regimen in gastrointestinal malignancies (6, 7). Despite its higher dose intensity, the bone marrow toxicity of HDFL is almost negligible (6, 8), thus making it an ideal regimen for whom intensive chemotherapy is not indicated. Indeed, in a group of AGC patients with poor general condition, we demonstrated that HDFL resulted in a 48% tumor response rate without eliciting any grade 3/4 leukopenia and thrombocytopenia (6).

HDFL, a non-myelosuppressive regimen with a moderately high activity against AGC, might be a safe and effective initial treatment for AGC patients presenting with acute DIC. Our initial experience in using HDFL for 5 such patients has been reported previously (9). Following HDFL treatment, all 5 patients with acute DIC improved, and 3 of them survived for more than 6 months. In this study, the merit of our initial findings was further assessed by analyzing data from an expanded cohort of patients diagnosed with AGC and acute DIC, and treated with HDFL.

Patients and Methods

Patients. Patients with a diagnosis of gastric cancer and DIC during the period 1994 to 2005 were identified from the database of the

Table I. *Pertinent clinicopathological characteristics.*

Characteristics	No. of patients	Percentage (%)
Total patients	19	100
Age		
Median (range) years	53 (31 ~ 72)	
Gender		
Male	11	58
Female	8	42
Onset of disease		
De novo metastatic	9	47
Recurrent form prior surgery	10	53
Prior adjuvant chemotherapy	4	21
Symptoms and signs of DIC		
Any	19	100
Muco-cutaneous	15	79
Gastro-intestinal tract	6	32
Genito-urinary tract	1	5
Intra-cranial	1	5
Microangiopathic hemolytic anemia	1	5
Histology		
Signet ring cell/poorly differentiated adenocarcinoma	13	68
Well and moderately differentiated adenocarcinoma	4	21
Not specified	2	11
Disease extent		
Stomach	9	47
Bone marrow	14	100[a]
Bone	13	68
Liver	3	16
Lung	2	11
Ovary	3	16

[a]Only 14 patients received bone marrow study.

Department of Medical Records of the National Taiwan University Hospital (Taipei, Taiwan). To be included in this analysis, the patients were required to meet the following criteria: histologically proven gastric carcinoma; the presence of symptoms and signs of a tendency to bleeding; thrombocytopenia (platelets <100 K/μl); positive DIC profiles, including decreased fibrinogen, increased D-dimer or increased fibrin degradation product (FDP) and no other causes responsible for the bleeding tendency, such as clinically overt infection or hereditary coagulopathy. In order to evaluate the effectiveness of HDFL as the initial treatment, only those patients receiving the HDFL regimen alone were included. The medical records of the included cases were reviewed to collect information about the presenting clinicopathological features, the details of chemotherapy, treatment response, survival time and causes of death.

At diagnosis, all of the patients were initially evaluated according to the procedures commonly used at our institute. In addition to clinical evaluation and blood testing for hemogram, biochemistry panel, and DIC profiles, the patients had undergone gastrointestinal pan-endoscopy, computed tomography (CT) of the abdomen and chest X-ray. Other studies, including isotope bone scan or bone marrow aspiration or biopsy, had been performed as indicated for symptomatic cases.

Table II. *Summary of laboratory data indicating acute DIC (N=19).*

Parameter	Median (range)	Normal range
Platelet count (K/μl)[a]	40 (4 ~ 83)	100 ~ 350
Fibrinogen (mg/dl)[b]	106 (30 ~ 349)	196 ~ 416
FDP (μg/dl)[c]	160 (10 ~ 1280)	<4
D-dimer (μg/ml)[d]	16 (4 ~ 64)	<0.3

[a]All (19) patients had platelet count evaluation; [b]15 patients received fibrinogen evaluation; [c]18 patients received FDP evaluation; [d]15 patients received D-dimer evaluation; FDP: fibrin degradation product.

Treatment. HDFL chemotherapy was given as a weekly, 24-h infusion of 5-FU 2600 mg/m^2 plus leucovorin 300 mg/m^2. The HDFL chemotherapy was continued until progression of disease or improvement of the acute DIC. When the acute DIC improved, the chemotherapy was intensified by combining HDFL with other cytotoxic agents, such as cisplatin, etoposide, or paclitaxel, at the discretion of the attending physician. The combination of cisplatin and HDFL was administered as follows: cisplatin 35 mg/m^2, 24h infusion, day 1 and 8; HDFL, day 1, 8, and 15, repeated every 28 days (10). The combination of paclitaxel and HDFL was administered as follows: paclitaxel 70 ~ 80 mg/m^2, 1h infusion, day 1, 8, and 15; HDFL, day 2, 9, and 16, repeated every 28 days (11). The combination of etoposide and HDFL was administered as follows: etoposide 65 mg/m^2, 2h infusion, day 1 to 3; HDFL, day 2, 9, and 16, repeated every 28 days (10).

Definition of response and survival. The response of the acute DIC to chemotherapy was evaluated by serial follow-up of clinical symptoms and signs, platelet count, and DIC profiles. A response of the acute DIC was defined as the combined finding of resolution of the tendency to bleeding, normalization of platelet counts (>100K/μl) and improvement of the DIC profiles. The overall survival was calculated from the start of chemotherapy to death due to any cause. The survival analysis was performed using the Kaplan-Meier method.

Results

Clinicopathological characteristics. A total of 19 AGC patients, who had presented with acute DIC and had initially been treated with HDFL, were identified between 1994 and 2005. Their pertinent clinico-pathological features are listed in Table I. Acute DIC was the presenting symptom which led to the diagnosis of recurrent or metastatic AGC in all the patients. The abnormal laboratory data indicating DIC at diagnosis are summarized in Table II. The median platelet count was 40K/μl (range: 4 ~ 83). The fibrinogen level was decreased in 14 of the 15 patients checked. The FDP and D-dimer were elevated in all of the 18 and 15 patients checked, respectively.

Treatment and response. The initial HDFL chemotherapy was continued for a median of 3 weeks (range: 1 ~ 10). All the patients also received supportive care for the bleeding tendency, including component therapy. Five of the patients

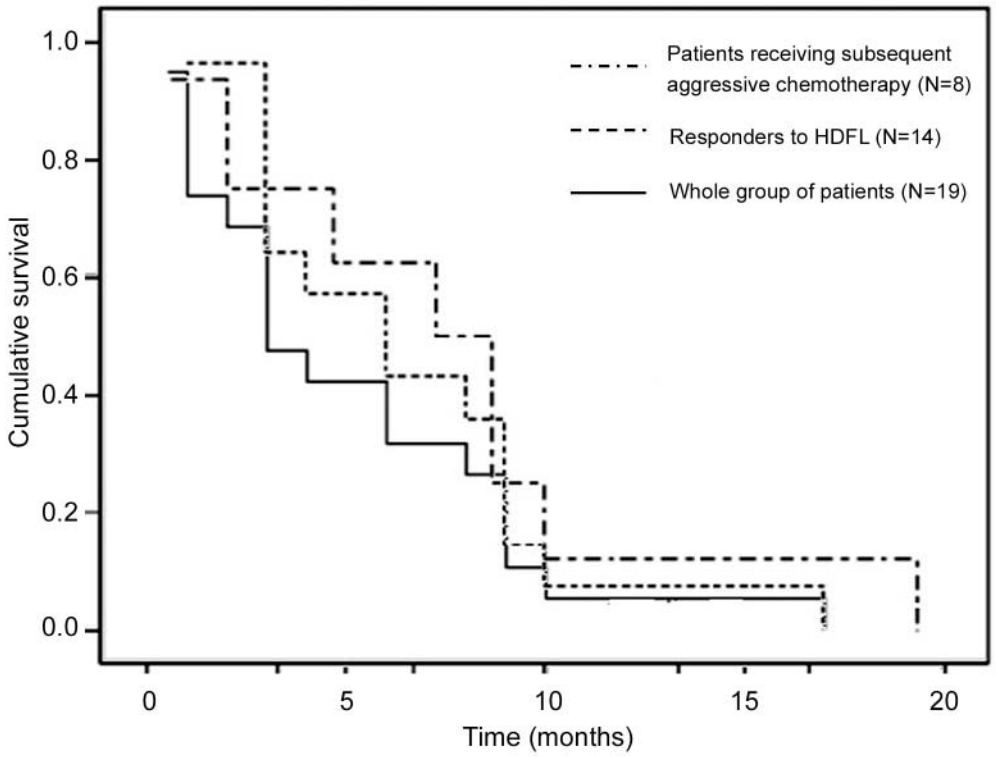

Figure 1. *Kaplan-Meier curves of overall survival of the whole group of patients, the responders to HDFL, and the patients who underwent subsequent aggressive chemotherapy.*

did not have a response of the DIC, 3 received only one dose of HDFL and 2 received 3 doses of HDFL. All of these nonresponders died within a very short period of time (range: 2～8 weeks) after diagnosis. The other 14 patients met the criteria for a response of the DIC. After a median of 4 weeks of HDFL, the platelet counts of these patients recovered to within the normal range, the abnormal laboratory data characteristic of DIC improved, and the clinical symptoms and signs of the bleeding tendency resolved. Subsequently, 8 out of the 14 responders received more aggressive combination chemotherapy. The combination regimens given to these patients were cisplatin plus HDFL in six patients, paclitaxel plus HDFL in one, and etoposide plus HDFL in one. The remaining six patients did not receive subsequent combination chemotherapy. Two of them were treated in early 1990s, when combination chemotherapy was still under development, two were of poor performance status due to a brain infarction and post-operation, respectively, and two were lost to follow-up.

The HDFL chemotherapy as the initial therapy was well tolerated by the AGC patients with acute DIC. There was no leukopenia or neutropenia. The non-hematological toxicities were almost negligible, except for HDFL-related hyperammonemic encephalopathy in one patient. This patient developed nausea, vomiting, and disturbed consciousness during the first infusion of HDFL. The hyperammonemic encephalopathy resolved completely after supportive care. This patient subsequently received no further chemotherapy, and died 2 weeks after the diagnosis.

Follow-up and survival. The recurrence of acute DIC was the major manifestation of disease progression for 12 of the 14 initial responders. The progression free survival was 3 months for the 14 responders, and 6 months for the 8 patients who received more aggressive combination chemotherapy following the initial HDFL. Among the 12 patients with recurrent acute DIC, 11 patients were unable to undergo further chemotherapy because of rapid deterioration of their general condition. Only one patient was able to undergo second-line chemotherapy. This patient was a 72-year-old man who had been initially treated with HDFL, followed by cisplatin-HDFL combination. Six months later when the disease progressed with recurrent acute DIC, he was given paclitaxel-HDFL combination as second-line treatment, which resulted in another remission for 1 month. This patient died 9 months after the initial diagnosis.

The median survival was 3 months (range: 0.5～17) for the whole group of patients, 6 months (range: 1～17) for the 14 responders, and 8 months for those who received more aggressive combination chemotherapy following the

initial HDFL treatment (Figure 1). At the time of this report, none of the patients was alive. The causes of death were related to acute DIC in 15 patients, and included the following: intracranial hemorrhage, massive cerebral infarction, pulmonary hemorrhage or emboli and acute DIC with multiple organ system failure in 7, 2, 2, and 4 patients, respectively. No patients died of treatment-related adverse events.

Discussion

This retrospective study of 19 AGC patients with acute DIC as the predominant feature confirmed that HDFL, a non-myelosuppressive dosing schedule of 5-FU, was a safe and effective first-line therapy. The effectiveness of HDFL was reflected by the fact that 14 out of the 19 (74%) patients had remission of the acute DIC, and half of them could subsequently receive combination chemotherapy regimens. Notably, the median survival time for the 8 patients who received combination chemotherapy after the initial treatment of HDFL was 8 months, which appeared to approximate that of AGS patients without acute DIC. The initial HDFL treatment alleviated the lethal condition of acute DIC and enabled a substantial group of patients to receive subsequent conventional chemotherapy for AGC with survival approximate to general AGC patients. Although this improvement may have resulted from patient selection at the time of the response of the DIC, it remains possible that HDFL contributed to a better outcome in the responders by controlling the underlying malignant process and the acute DIC.

With a similar approach to the present study, Toker *et al.* (12) used continuous infusion of 5-FU (200 mg/m^2/day), another non-myelosuppressive dosing schedule of 5-FU, as the initial treatment for AGC patients presenting with acute DIC. Among the 6 cases they reported, 5 had a dramatic improvement of clinical status and DIC within 2 weeks, and could subsequently receive a combination regimen based on epirubicin, cisplatin, and 5-FU (the ECF regimen). Nevertheless, while the selected patients enjoyed longer survival (up to 32 weeks), the overall survival time of the whole group of patients remained relatively short (15 weeks).

The other possible treatment approach for AGC patients with acute DIC is up-front combination chemotherapy (13). However, this approach needs a careful design because the increased efficacy of combination chemotherapy might be negated by the increased treatment-related toxicity. Previously, Chao *et al.* (14) reported a study of a combination of etoposide, epirubicin, cisplatin, an HDFL-like regimen, as the first-line therapy in patients with AGC and acute DIC. When etoposide, epirubicin, and cisplatin were given in a weekly and reduced-dose schedule (etoposide, 40 mg/m^2/week, epirubicin 10 mg/m^2/week, cisplatin 25 mg/m^2/week), six such patients were safely treated. However, the survival time of their patients, ranging from 12 to 32 weeks, was similar to that of the currently reported cohort. Whether the incorporation of other active chemotherapy agents against AGC such as taxanes, oxaliplatin, and irinotecan would improve the outcome of these patients warrants further investigation.

Finally, this study, which included the largest case series reported to date, confirmed several special clinicopathological features of this disease entity. In agreement with previous reports, AGC with acute DIC was commonly associated with undifferentiated adenocarcinoma and a relatively younger population (3, 12, 15, 16). The uniqueness of this disease entity was also shown in the preferential involvement of bone marrow and bone and the rare involvement of extraosseous organs. A better understanding of the pathogenetic mechanism underlying these unique presentations may help the development of novel therapies for this disease entity in the future.

In conclusion, the initial treatment of HDFL is safe and effective in reversing DIC for AGC patients presenting with acute DIC. In selected patients who respond to this initial treatment, subsequent combination chemotherapy may improve survival.

Acknowledgements

The study was supported by grant DOH95-TD-B-111-001 from the Department of Health, Executive Yuan, Taipei, Taiwan, and grant NTUH-96S-597 from National Taiwan University Hospital, Taipei, Taiwan, R.O.C.

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Received November 27, 2007
Revised January 29, 2008
Accepted February 15, 2008