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/m² plus leucovorin 300 mg/m², 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).

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/m² plus leucovorin 300 mg/m², 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
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 clinicopathological 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. The fibrinogen evaluation; c18 patients received FDP evaluation; d15 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/m² plus leucovorin 300 mg/m². 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/m², 24h infusion of 5-FU 2600 mg/m² plus leucovorin 300 mg/m². 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/m²; 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/m², 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/m², 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. 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...
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/m²/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/m²/week, epirubicin 10 mg/m²/week, cisplatin 25 mg/m²/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.

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References


