Original Article

Chemotherapy in Advanced Gastric Cancer Patients Associated with Disseminated Intravascular Coagulation

In Gyu Hwang, MD, PhD[1]
Jin Hwa Choi, MD, MS[2]
Se Hoon Park, MD, PhD[3]
Sung Yong Oh, MD, PhD[4]
Hyuk-Chan Kwon, MD, PhD[4]
Soon Il Lee, MD, PhD[5]
Do Hyoung Lim, MD[5]
Gyeong-Won Lee, MD, PhD[6]
Jung Hun Kang, MD, PhD[6]

[1]Department of Internal Medicine,
Chung-Ang University
College of Medicine, Seoul,
[2]Department of Radiation Oncology,
Chung-Ang University Hospital,
Chung-Ang University
College of Medicine, Seoul,
[3]Department of Internal Medicine,
Samsung Medical Center,
Sungkyunkwan University
School of Medicine, Seoul,
[4]Department of Internal Medicine,
Dong-A University Hospital,
Dong-A University College of Medicine, Busan,
[5]Department of Internal Medicine,
Dankook University Hospital,
Dankook University College of Medicine,
Cheonan, [6]Department of Internal Medicine,
Institute of Health Science,
Gyeongsang National University
School of Medicine, Jinju, Korea

+ + + + + + + + + + + + + + +
Correspondence: Jung Hun Kang, PhD
Department of Internal Medicine,
Institute of Health Science,
Gyeongsang National University
School of Medicine, 79 Gangnam-ro,
Jinju 660-702, Korea
Tel: 82-55-750-8063
Fax: 82-55-758-9122
E-mail: newatp@naver.com

Purpose

Little is known about the clinical features of advanced gastric cancer (AGC) combined with disseminated intravascular coagulation (DIC). The main objective of this study was to determine the clinical outcome of patients with AGC complicated by DIC.

Materials and Methods

We conducted a retrospective review of 68 AGC patients diagnosed with DIC at four tertiary medical centers between January 1995 and June 2010.

Results

Sixty eight patients were included. The median age was 55 years (range, 25 to 78 years). Nineteen patients received chemotherapy, whereas 49 patients received only best supportive care (BSC). The median overall survival (OS) of the 68 patients was 16 days (95% confidence interval [CI], 11 to 21 days). Significantly prolonged OS was observed in the chemotherapy group, with a median survival of 61 days compared to 9 days in the BSC group (p<0.001, log-rank test). Age and previous chemotherapy were another significant factors that were associated with OS in univariate analysis. In multivariate analysis, age (≥65 vs. <65; hazard ratio [HR], 0.38; 95% CI, 0.18 to 0.78; p<0.001), chemotherapy (BSC vs. chemotherapy; HR 0.31; 95% CI, 0.15 to 0.63; p<0.001), and previous chemotherapy (yes or no; HR, 0.49; 95% CI, 0.25 to 0.98; p<0.045) were consistently independent prognostic factors that impacted OS.

Conclusion

Our study showed that patients with AGC complicated by DIC had very poor OS, and suggested that chemotherapy might improve OS of these patients.

Introduction

Gastric cancer ranks fourth in cancer incidence in men (640,600 new cases per year) and fifth in women (349,000 new cases per year) [1]. Advanced gastric cancer (AGC) is rarely associated with disseminated intravascular coagulation (DIC); the incidence rate of DIC is 1.6% in AGC patients [2]. Due to its rarity, little is known about the clinical features of patients with AGC and DIC.

DIC is a clinical condition characterized by widespread activation of the coagulation system. It can be caused by various precipitating conditions; trauma, sepsis, toxin, and solid tumors have all been reported to induce DIC complications [3]. DIC from cancer generally has a less fulminant course and follows a more gradual and chronic pattern than DIC complicating sepsis or trauma. However, chronic activation of the coagulation system eventually leads to exhaustion of platelets and coagulation factors and can result in development of a clinical hemorrhagic problem [4].

The prognosis of symptomatic DIC associated with AGC is known to be very poor [5]. Treatment of underlying malignancy is a key measure for restoration of normal coagulation. If the malignancy is improved, then the DIC will usually diminish with time. However, patients often have a poor performance status (PS) accompanied by hematologic abnormalities such as thrombocytopenia, leucopenia, and anemia in AGC associated with DIC. These conditions cause physicians to be hesitant in starting chemotherapy and cause a dilemma in treatment of AGC complicated by DIC. It also may be misinterpreted as a simple hematologic abnormality or long-lasting hematologic toxicity caused by previous chemotherapy in the early stage, resulting in delayed treatment and subsequent aggravation of prognosis. Therefore, knowledge of the disease course is imperative.

Although anecdotal cases and several small studies indicating that the prognosis of AGC associated with DIC might improve with 5-fluorouracil (5-FU) based chemotherapy have been reported [2,6-10], the clinical data are far from sufficient for establishment of a standardized treatment strategy. The main objective of this multicenter retrospective study was to determine the clinical outcome of AGC complicated by DIC. The secondary aim was to identify prognostic factors having an impact on survival.

Materials and Methods

1. Patient eligibility and assessments

Patients were eligible for inclusion in this retrospective study if they had histologically confirmed gastric cancer with at least one metastatic site and if they met the DIC criteria of the Japanese Association for Acute Medicine (JAAM) [11]. DIC was diagnosed in patients with ≥ 4 points, according to the JAAM criteria [11,12].

Patients were identified at four tertiary medical centers between December 1994 and April 2010. Demographic information, including age, sex, PS, and clinical data, including clinicopathologic features and laboratory findings were collected. Laboratory information included a complete blood count, chemistry panel, carcinoembryonic antigen, and DIC profiles. Radiologic images included chest radiographs, and abdominal and/or chest computed tomography (CT) containing measurable lesions were considered baseline images if they were obtained less than four weeks before starting chemotherapy. Medical records and abdominal and/or chest CTs were reviewed for evaluation of the clinical course and outcomes of chemotherapy. Responses to chemotherapy were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) based on changes in target lesions and non-target lesions [13].

2. Chemotherapy regimens

All eligible patients received one of the following chemotherapy regimens: A institute—FOLFOX: oxaliplatin 85 mg/m² (day [D] 1), leucovorin 30 mg (D1, 2), 5-FU 1,000 mg/m² (D1, 2) every two weeks, DCF: docetaxel 70 mg/m² (D1), cisplatin 40 mg/m² (D2, 3), 5-FU 1,200 mg/m² (D1, 2, 3) every three weeks, FOLFIRI: irinotecan 180 mg/m² (D1), leucovorin 30 mg (D1, 2), 5-FU 1,000 mg/m² (D1, 2) every two weeks, docetaxel: docetaxel 30 mg/m² (D1, 8) every three weeks, DP: docetaxel 75 mg/m² (D1), cisplatin 60 mg/m² (D1) every three weeks; B institute—DP: docetaxel 75 mg/m² (D1), cisplatin 75 mg/m² (D1) every three weeks; C institute—TP: paclitaxel 175 mg/m² (D1), cisplatin 80 mg/m² (D1) every three weeks, FOLFIRI: irinotecan 150 mg/m² (D1, leucovorin 20 mg/m² (D1, 2), 5-FU 400 mg/m² intravenous (IV) push (D1, 2), 5-FU 600 mg/m² over 22 hours (D1, 2) every two weeks; D institute—FPL: leucovorin 20 mg/m² IV push (D1-D5), 5-FU 800 mg/m² (D1-D5), cisplatin 75 mg/m² (D1), every three weeks, docetaxel: docetaxel 75 mg/m² (D1) every three weeks, FL: leucovorin 20 mg/m² IV push (D1-D5), 5-FU 800 mg/m² (D1-D5) every three weeks, DP: docetaxel 75 mg/m² (D1), cisplatin 75 mg/m² (D1) every three weeks.

Standard pre-medications were administered appropriately prior to treatment depending on the protocol of the specific institution. Relative dose intensity (RDI) was defined as the actual chemotherapeutic dose administered divided by the total planned dose in a given period.

Table 1. Patient characteristics

Characteristic	Total (n=68)	Chemotherapy (n=19)	BSC (n=49)	p-value[a]
Gender				0.17
Male	39 (57)	8 (42)	31 (63)	
Female	29 (43)	11 (58)	18 (37)	
Age (yr)				0.03
Median	55 (25-78)	51 (25-68)	58 (26-78)	
PS				0.09
0-1	23 (34)	3 (16)	20 (41)	
2-4	45 (66)	16 (84)	29 (59)	
Histology				0.98
Well differentiated	1 (1)	0 (0)	1 (2)	
Moderate differentiated	10 (15)	2 (11)	8 (16)	
Poorly differentiated	26 (38)	7 (37)	19 (39)	
Signet ring cell	17 (25)	9 (47)	8 (16)	
Not specified	14 (21)	1 (5)	13 (27)	
Hemoglobin level (g/dL)				0.08
<8	18 (27)	6 (32)	12 (24)	
8-10	28 (41)	11 (58)	17 (35)	
>10	22 (32)	2 (10)	20 (41)	
Platelet count ($\times 10^3$/μL)				0.27
<25	19 (28)	6 (32)	13 (26)	
25-75	32 (47)	11 (58)	21 (43)	
>75	17 (25)	2 (10)	15 (31)	
Prothrombin time (INR)				<0.01
<1.5	33 (49)	14 (74)	19 (39)	
≥1.5	35 (51)	5 (26)	30 (61)	
Bone metastasis				<0.01
Yes	29 (43)	15 (79)	14 (29)	
No	39 (57)	4 (21)	35 (71)	
No. of metastatic sites				0.84
Single	30 (44)	8 (42)	22 (45)	
Multiple	38 (56)	11 (58)	27 (55)	
Previous chemotherapy				<0.01
No	19 (28)	10 (53)	9 (18)	
Yes	49 (72)	9 (47)	40 (82)	

Values are presented as number (%). BSC, best supportive care; PS, performance status; INR, international normalized ratio.
[a]p-values are for comparison between BSC and chemotherapy.

3. Statistical analysis

Baseline demographics, including medians, ranges, and frequencies were summarized using descriptive statistics. Patients were divided into a chemotherapy group and a best supportive care (BSC) group. A chi-squared test or Fisher's exact test were used as appropriate for comparison of categorical variables (sex, site, metastatic site, PS), and a Wilcoxon rank sum test was used for comparison of quantitative variables (age) between the two groups.

Survival was calculated according to the Kaplan-Meier method and the survival curves were compared by univariate analysis with the long-rank test. Cox's proportional hazard model was used for multivariate survival analyses. Overall survival (OS) was defined as the time from the date of first chemotherapy administration to the date of death. Statistical significance was defined as a p-value<0.05. All analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL) or SAS ver. 9.2 (SAS Institute Inc., Cary, NC).
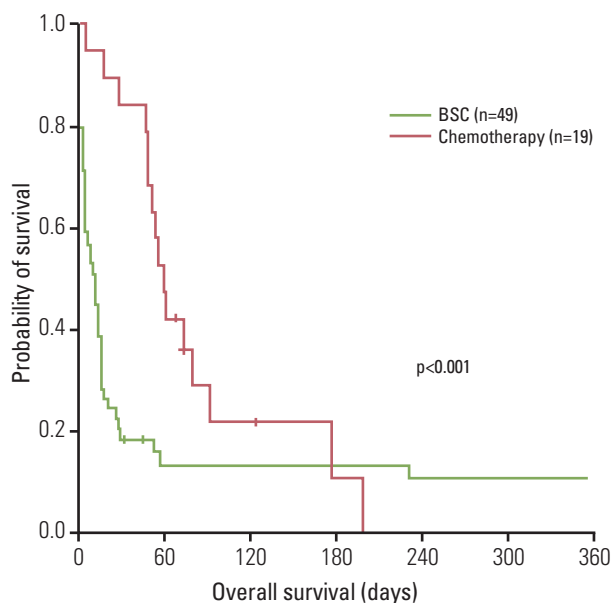
Fig. 1. Overall survival. Patients undergoing chemotherapy had a significantly longer overall survival than best supportive care (BSC) patients (median, 61 days vs. 9 days; p < 0.001).

Results

1. Patient characteristics

A total of 68 patients were enrolled in this study. A description of the clinical characteristics of the patients is provided in Table 1. Nineteen patients (28%) underwent chemotherapy, while 49 patients (72%) received only BSC. Of the 19 patients who underwent chemotherapy, nine (47%) were treated with 5-FU-based chemotherapy and 10 (53%) were treated with taxane-based chemotherapy. The median age of patients was 55 years (range, 25 to 78 years). Patients who received chemotherapy were significantly younger than patients in the BSC group (51 years vs. 58 years, p=0.03). More frequent bone metastasis (79% vs. 29%, p < 0.01), previous chemotherapy (63% vs. 18%, p < 0.01) and prolonged prothrombin time (61% vs. 26%, p < 0.01) were observed in the chemotherapy group. No significant difference in other factors, including sex, PS, baseline hemoglobin, platelet count, and lactate dehydrogenase level was observed between the two groups. The median follow-up duration was 0.5 months (range, 0.3 to 0.7 months).

2. Therapeutic outcomes and prognostic factors

A total of 47 cycles (median, 2 cycles) were delivered to patients in the chemotherapy group. The mean dose intensitiesand RDIs were 1,077.99 mg /m²/wk (range, 750 to 1,333.3 mg/m²/wk) and 95.8% for 5-FU-based regimens and 24.25 mg/m²/wk (range, 23.3 to 25 mg/m²/wk) and 100% for taxane-based regimens. Of the 19 chemotherapy patients, only seven could be assessed for their responses. Two patients (10.5%) had partial responses, one patient (5.2%) had stable disease, and four patients (21.0%) had progressive disease.

Among the patients who underwent chemotherapy, DIC-related symptoms showed improvement in eight patients (42%). The median OS was 16 days (95% CI, 11 to 21 days). Patients undergoing chemotherapy had a significantly longer OS (median, 61 days; 95% CI, 50 to 72 days; p < 0.001) than BSC patients (median, 9 days; 95% CI, 6 to 16 days) (Fig. 1).

According to univariate analysis, younger age (cut off value; 65 years, p < 0.001), chemotherapy (p < 0.001), and previous chemotherapy (p < 0.001) showed an association with superior survival. However, no statistically significant differences were observed with regard to gender, PS, histology, prothrombin time, number of metastases, baseline hemoglobin, platelet count, fibrinogen, alkaline phosphatase, and chemotherapy regimen. On multivariate analysis, chemotherapy (p < 0.001; hazard ratio [HR], 0.31), younger age (p < 0.001; HR, 0.38) and previous chemotherapy (p < 0.045; HR, 0.49) showed an independent association with a longer OS (Table 2).

Discussion

Our study included the largest number of patients with AGC complicated by DIC to date, and also compared clinical outcomes between a chemotherapy group and a BSC group. Although similar studies on these issues have been reported, those studies included a small number of cases or only evaluated treatment outcomes (Table 3).

We found that patients who underwent chemotherapy had outcomes superior to those who received BSC. Our finding is consistent with the report by Rhee et al. [14], which favored chemotherapy in AGC patients with DIC. Until now, that was the only study comparing a chemotherapy group with a BSC group [14]. However, that study included only seven patients in the BSC group, which weakens the conclusion that chemotherapy provides superior outcomes to BSC in AGC with DIC. In our study, we included 49 patients in the

Table 2. Multivariate analysis for overall survival

Factor	Stratification	HR	95% CI	p-value[a]
Age (yr)	< 65	0.38	0.18-0.78	< 0.001
	≥ 65	1		
Chemotherapy	Yes	0.31	0.15-0.63	< 0.001
	No	1		
Prothrombin (INR)	< 1.5	0.88	0.53-1.71	0.880
	≥ 1.5			
PS	0-2	0.72	0.42-1.54	0.507
	3-4	1		
Bone metastasis	No	0.95	0.51-1.74	0.861
	Yes	1		
Previous chemotherapy	No	0.49	0.25-0.98	0.04
	Yes	1		

HR, hazard ratio; CI, confidence interval; INR, international normalized ratio; PS, performance status. [a]Cox proportional hazard regression model.

Table 3. Studies or case series on AGC with DIC

Authors	No. of cases	Regimen	No. of responses to CTX	Comparison with BSC group	PFS (days)	OS (days)
Chao et al. [6]	6	5-FU based	4 (67)	No	N/A	196
Tokar et al. [9]	6	5-FU based	5 (83)	No	N/A	105[a]
Yeh and Cheng [7]	5	5-FU based	3 (60)	No	N/A	N/A
Huang et al. [8]	19	5-FU based	14 (74)	No	90	90
Takashima et al. [2]	22	5-FU based	17 (77)	No	98	154
Rhee et al. [14]	21	Various regimens	2 (18)	Yes	N/A	58
Present case	68	Various regimens	2 (11)	Yes	N/A	16

Values are presented as number (%). AGC, advanced gastric cancer; DIC, disseminated intravascular coagulation; CTX, chemotherapy; BSC, best supportive care; PFS, progression free survival; OS, overall survival; 5-FU, 5-fluorouracil; N/A, not available or not applicable. [a]Survival was reported as mean value.

BSC group, which strengthens our assertion that chemotherapy can prolong survival in patients with AGC and DIC. Other studies without BSC also reported higher responses to chemotherapeutic treatment, from 74% to 100% of cases, and favorable survival times, which supports the notion that chemotherapy could be beneficial to patients with AGC complicated by DIC [2,6-10]. In addition, although statistical significance was marginal (p=0.045), patients who had not undergone prior chemotherapy had better survival than those who had undergone previous chemotherapy.

In our current study, the median OS (16 days) was very poor. Compared with other studies, the poorest survival was observed in this study [2,6-10]. In this study, patients with BSC had a median OS of only nine days. As reported in previous studies, we assert that this short life expectancy reflects the aggressive nature of AGC with DIC [5]. However, in this study, selection bias may have contributed to the relatively poorer survival. The patient cohort was comprised of poor PS (proportion of PS 2-4 was 66%) and the majority of patients were in the BSC group (72%). Because other studies on AGC with DIC usually included only patients who underwent chemotherapy [2,6-10], this selection bias could have resulted in the difference in survival.

Biopsy reports showed that the majority (80%) of patient cohort in our study had signet ring cells (SRC) or poorly differentiated cells (PD) type and this result is similar to another studies [7,8,15]. Considering the fact that SRC and PD are not major histologic types of gastric cancer [16], this may be a notable finding. Conduct of future studies on the association between the histologic type of gastric cancer and DIC is warranted.

There are several limitations to this study. First, due to the inherent nature of retrospective studies and limited accessibility to all of the centers, we were unable to fully identify

changes in the clinical manifestations of the disease or adverse effects of chemotherapy. The information collected on chemotherapy was not sufficient. Because patients were recruited regardless of treatment status in the trajectory of gastric cancer, the possibility exists that a high proportion of patients were receiving salvage chemotherapy at the time of their diagnosis with DIC, which may have contributed to the poor survival of our cohort. In addition, although cases were recruited from six tertiary cancer centers, the patient cohort was not sufficient to determine whether chemotherapy is really helpful for gastric cancer patients with DIC.

Conclusion

Findings of our study suggest that AGC patients with DIC could benefit from chemotherapy. Therefore, chemotherapy maybe considered among the first treatment options in AGC patients who also present with DIC.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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