ORIGINAL ARTICLE

Gut and Liver, Vol. 7, No. 3, May 2013, pp. 363-370

Use of Antithrombin and Thrombomodulin in the Management of Disseminated Intravascular Coagulation in Patients with Acute Cholangitis

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Background/Aims: To evaluate the usefulness and safety of treating disseminated intravascular coagulation (DIC) complicating cholangitis primarily with antithrombin (AT) and thrombomodulin (rTM). **Methods:** A DIC treatment algorithm was determined on the basis of plasma AT III levels at the time of DIC diagnosis and DIC score changes on treatment day 3. Laboratory data and DIC scores were assessed prospectively at 2-day intervals. **Results:** DIC reversal rates >75% were attained on day 7. In the DIC reversal group, statistically significant differences from baseline were observed in interleukin-6 and C-reactive protein levels within 5 days. Patients with no DIC score improvements after treatment with AT alone experienced slow improvement on a subsequent combination therapy with rTM. Although a subgroup with biliary drainage showed greater improvement in DIC scores than did the nondrainage subgroup, the mean DIC score showed improvement even in the nondrainage subgroup alone. Gastric cancer bleeding that was treated conservatively occurred in one patient. As for day 28 outcomes, three patients died from concurrent malignancies. **Conclusions:** Although this algorithm was found to be useful and safe for DIC patients with cholangitis, it may be better to administer rTM and AT simultaneously from day 1 if the plasma AT III level is less than 70%. **(Gut Liver 2013;7:363-370)**

Key Words: Disseminated intravascular coagulation; Cholangitis; Antithrombins; Thrombomodulin

INTRODUCTION

Excluding the treatment of the underlying disease, anticoagulants are the first-line therapy recommended in the Japanese Guideline for treatment of disseminated intravascular coagulation (DIC) caused by infections.[1] In the guideline, nevertheless, recombinant human soluble thrombomodulin (rTM), a novel agent for DIC, which first became available in Japan in 2008, is not cited. The proper use of rTM in combination with antithrombin (AT) and other currently used drugs for the treatment of DIC, and the safety and usefulness of combination therapy with rTM remain unclear.

Acute cholangitis (AC) is frequently complicated by DIC, a syndrome with a poor prognosis in severe cases. However, there have been few reports focusing on DIC treatment in AC.

Thus, we have devised an original algorithm of treatment primarily with AT and rTM that corresponds to changes in a patient's clinical status over time, which is minimally cumbersome. DIC was treated in patients with AC at our department employing this algorithm, whereby hematologic/blood biochemical data and changes in DIC score over time were evaluated to examine the usefulness and safety. This is the first part of a collective report on clinical experiences with rTM in the treatment of DIC complicating AC.

MATERIALS AND METHODS

1. Treatment algorithm for DIC

An algorithm for DIC treatment was developed on the basis of baseline plasma AT III level at the time of DIC diagnosis. On the basis of this algorithm, 1) AT was administered at 1,500 units/day for 3 days to patients showing a baseline plasma AT III level ≤69%. When there was still no improvement in score, as determined in accordance with the Japanese acute phase DIC diagnostic criteria (Table 1),[2] treatment with an rTM preparation at 380 units/kg/day was initiated on day 3; or 2) rTM at this dose was administered to patients with baseline plasma AT III levels ≥70%. AT administration of was terminated as deemed appro-

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Received on May 10, 2012. Revised on July 12, 2012. Accepted on July 27, 2012. Published online on April 25, 2013.
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl.2013.7.3.363

priate when plasma AT III level was restored to ≥70%, and no additional AT treatment was administered even when plasma AT III level decreased to <70% during the treatment course, insofar as DIC score tended to improve. The rTM was administered at 130 units/kg/day in patients with renal dysfunction. The rTM preparation was administered intravenously over 30 minutes once daily, basically for 6 consecutive days. DIC treatment algorithms are summarized in Figs. 1 and 2. No heparin preparation was used because the anti-inflammatory effect of AT was inhibited by the concomitant use of heparin and because there was concern about adverse hemorrhagic reactions during treatment with multiple anticoagulants. No restriction was placed on other medications other than heparin for DIC, which were left to the discretion of attending physicians. Biliary drainage was performed as required according to the patient's condition, again on the basis of the attending physician's assessment. This study was conducted with the approval of the Ethics Committee of St. Marianna University School of Medicine Hospital.

Table 1. Disseminated Intravascular Coagulation Diagnostic Criteria Defined by the Japanese Association for Acute Medicine

	Score
Systemic inflammatory response syndrome (SIRS) criteria	
≥3	1
0–2	0
Platelet count, $\times 10^9$/L	
<80% or >50% decrease within 24 hr	3
≥80% and >120%; or >30% decrease within 24 hr	1
≥120	0
Prothrombin time (value of patient/nomal value)	
≥1.2	1
<1.2	0
Fibrin/fibrinogen degradation products, mg/L^{-1}	
≥25	3
≥10 and <25	1
<10	0
Diagnosis	
≥4 points	DIC

Fever of more than 38°C or less than 36°C. Heart rate of more than 90 beats per minute. Respiratory rate of more than 20 breaths per minutes or a $PaCO_2$ level of less than 32 mm Hg. Abnomal white blood cell count (>12,000/μL or <4,000/μL or >10% bands).

2. Patients

The study population consisted of 14 patients with AC complicated by DIC diagnosed at our department between April 2010 and March 2011. There were nine men and five women with a mean age of 72.5±8.4 years. Fourteen patients had AC; severe in 12 and moderate in two, as determined in accordance with the Japanese version of the Guideline for the Management of Acute Cholangitis (Table 2). The primary diseases underlying AC included malignant biliary tract stenosis in eight patients (carcinoma of the pancreatic head in five; bile duct carcinoma, hepatocellular carcinoma, and lymph node metastasis of gastric cancer in one each) and choledocholithiasis in six patients. DIC was diagnosed in accordance with the diagnostic criteria for acute-phase DIC (i.e., conditions were scored ≥4) (Table 1).[2] The DIC score at the time of diagnosis was four in five patients, five in three, six in four, seven in one, and eight in one. On the basis of the treatment algorithm, six patients were categorized into the AT-treated group, two into the rTM-treated group, and six into the group treated with the combination regimen of AT and rTM (AT+rTM-treated group). Other drugs administered concomitantly for DIC were gabexate mesilate in 13 patients and ulinastatin in four (including duplications). Endoscopic biliary drainage was performed in seven patients (endoscopic nasobiliary drainage [ENBD] in five and endoscopic biliary stenting (EBS) in two patients). Patient background characteristics are summa-

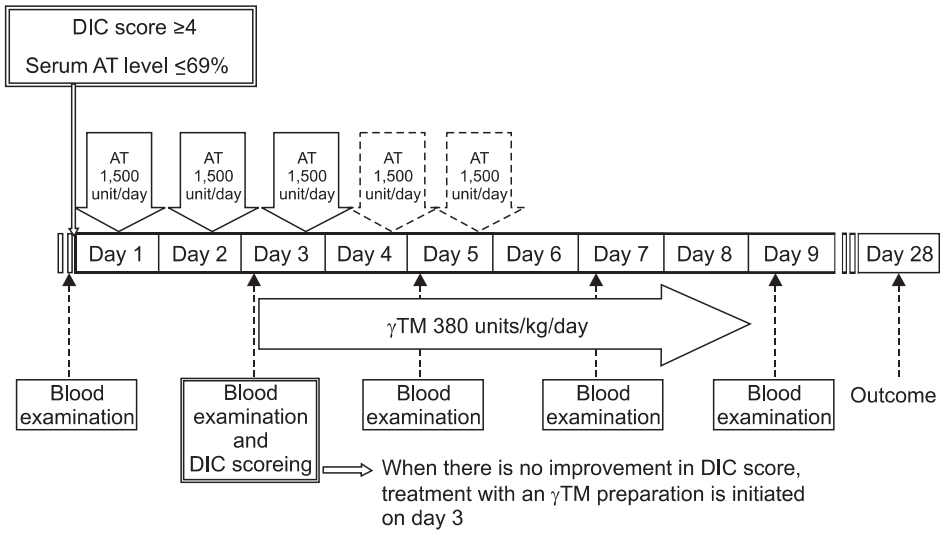

Fig. 1. Disseminated intravascular coagulation (DIC) treatment algorithm for patients with a baseline plasma antithrombin (AT) III level <69%.
γTM, thrombomodulin.

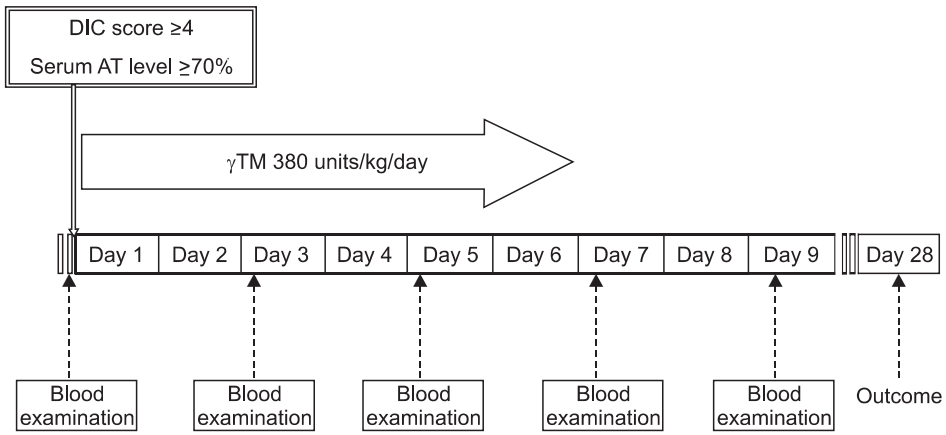

Fig. 2. Disseminated intravascular coagulation (DIC) treatment algorithm for patients with a baseline plasma antithrombin (AT) III level >70%.
γTM, thrombomodulin.

Table 2. The Severity Assessment Criteria for Acute Cholangitis of the Japanese Ministry of Health, Labor, and Welfare

"Severe" acute cholangitis is defined as acute cholangitis that is associated with at least one of the following factors:

1. Shock
2. Bacteremia
3. Disturbance of consciousness
4. Acute renal failure

"Moderate" acute cholangitis is defined as acute cholangitis that is associated with at least one of the following factors:

1. Jaundice (total serum bilirubin >2.0 mg/dL)
2. Hypoalbuminemia (serum albumin <3.0 g/dL)
3. Renal dysfunction (serum creatinine >1.5 mg/dL, serum urea nitrogen >20 mg/dL)
4. Throm bopenia (blood platelet count <120,000/mm^3)
5. Fever with temperatures above 39 degrees Celsius

"Mild" acute cholangitis is that which does not meet the criteria for "severe" or "moderate" acute cholangitis.

rized in Table 3.

3. Measurements

Taking the day of DIC diagnosis (treatment initiation day) as day 1, hematological/blood biochemical test findings (platelet count and levels of fibrin/fibrinogen degradation products [FDP], prothrombin time-international normalized ratio [PT-INR], fibrinogen [Fib], AT III, C-reactive protein [CRP], high mobility group box 1 [HMGB-1], and interleukin-6 [IL-6]) and DIC scores determined on the basis of the acute-phase DIC diagnostic criteria were assessed prospectively on days 1, 3, 5, 7, and 9 to verify therapeutic results on the basis of this treatment algorithm. Patients showing DIC score improvement to <3 were defined as the DIC reversal group. On the other hand, those showing DIC scores that remained at ≥4 were defined as the persistent DIC group. Therapeutic results were also assessed by comparison between the DIC reversal group and the persistent DIC group, among the AT-, rTM-, and AT+rTM-treated groups, and between biliary drainage and nondrainage groups. The patients were also assessed in terms of adverse events and clinical outcomes on day 28.

Platelet count and the levels of FDP, PT-INR, Fib, AT III, and CRP were measured as routine tests at our Central Clinical Laboratory. Samples for the determination of HMGB-1 and IL-6 levels were stored frozen at -80°C, and HMGB-1 level was assayed by ELISA (HMGB-1 ELISA Kit 2; Shino-Test Co., Kanagawa, Japan) and IL-6 level by CLEIRA (Quanti Glo Human IL-6 Immunoassay 2nd Generation; R&D Systems, MN, Minneapolis, USA).

4. Statistical analyse

Statistical analysis was carried out using the Prism5 program (GraphPad Software Inc., La Jolla, CA, USA). Intergroup comparison of median values of the hematological/blood chemical test parameters was performed using the Wilcoxon signed rank test. With respect to group mean DIC scores, the unpaired t-test with Welch's correction was carried out to compare between two groups, and one-way factorial ANOVA and multiple comparison tests were conducted to compare among three groups. Any intergroup differences found were considered to be statistically significant at $p<0.05$.

RESULTS

1. Time courses of changes in serum parameters and DIC score

The day of DIC diagnosis (treatment initiation day) was taken as day 1 for clarity. The median values of hematological/blood biochemical test results on days 1, 3, 5, 7, and 9 were respectively as follows: platelet counts, 9.7, 8.7, 9.7, 13.7, and $16.6\times10^4/\mu L$; FDP levels, 81.6, 66.2, 38.6, 25.1, and 26.1 μg/mL; PT-INR levels, 1.4, 1.3, 1.3, 1.3, and 1.3; Fib levels, 274, 345, 326, 325, and 295 mg/dL; AT III levels, 56%, 79%, 80%, 74%, and 70%; CRP levels, 11.9, 11.0, 5.3, 4.5, and 3.8 mg/dL; HMGB-1 levels, 15.7, 11.4, 10.6, 7.8, and 10.4 ng/mL; and IL-6 levels, 15,111.6, 106.0, 39.9, 34.3, and 36.5 pg/mL (Fig. 3).

Table 3. Patients Background Characteristics

Case	Diagnosis	Severity of acute cholangitis	DIC score	The dosing period of AT, day	The dosing period of rTM, day	Other medications for DIC	Biliary drainage
1	Pancreatic cancer	Severe	4	3	-	GM	-
2	Hepatocelluler carcinoma	Severe	4	5	-	GM, US	ENBD
3	Choledocholithiasis	Severe	5	3	3	GM	-
4	Pancreatic cancer	Severe	7	5	6	GM, US	-
5	Gastric cancer Lymph node metastasis	Severe	4	-	6	GM, US	-
6	Pancreatic cancer	Mild	7	3	6	GM	-
7	Choledocholithiasis	Severe	6	3	-	GM	ENBD
8	Pancreatic cancer	Mild	4	3	6	-	-
9	Choledocholithiasis	Severe	5	3	-	GM	ENBD
10	Cholangiocarcinoma	Severe	6	3	3	GM, US	ENBD
11	Choledocholithiasis	Severe	4	3	-	GM	ENBD
12	Choledocholithiasis	Severe	5	3	6	GM	EBS
13	Pancreatic cancer	Severe	6	3	-	GM	-
14	Choledocholithiasis	Severe	6	-	6	GM	EBS

DIC, disseminated intravascular coagulation; AT, antithrombin; rTM, thrombomodulin; GM, gabexate mesilate; US, ulinastatin; ENBD, endoscopic nasobiliary drainage; EBS, endoscopic biliary stenting.

Comparison between days 1 and 9 revealed statistically significant improvements in levels of CRP ($p<0.01$) and IL-6 ($p=0.02$). Mean acute-phase DIC score over time showed improvement, i.e., 5.3, 3.1, 2.6, 2.2, and 2.2 (Fig. 4), with a statistically significant difference between days 1 and 9 ($p<0.01$). The DIC reversal rate on days 9 was 78.6%.

2. Comparison between DIC reversal and persistent DIC groups

Median values of hematological/blood biochemical test results on days 1, 3, 5, 7, and 9 in the DIC reversal group (n=11) were respectively as follows: platelet counts, 9.7, 9.2, 13.2, 18.3, and $19.7\times10^4/\mu L$; FDP levels, 23.1, 8.1, 8.2, 8.2, and 12.8 μg/mL; PT-INR levels, 1.3, 1.1, 1.1, 1.1, and 1.1; Fib levels, 297.0, 395.0, 373.0, 407.0, and 329.5 mg/dL; AT III levels, 59.0%, 81.0%, 84.0%, 78.0%, and 71.0%; CRP levels, 15.6, 10.2, 4.0, 3.2, and 2.8 mg/dL; HMGB-1 levels, 17.5, 10.8, 9.1, 7.8, and 8.8 ng/mL; and IL-6 levels, 405.0, 44.1, 18.3, 15.7, and 16.6 pg/mL (Fig. 5). Comparison between days 1 and 9 revealed statistically significant improvements in the levels of CRP ($p<0.01$), HMGB-1 ($p=0.03$), and IL-6 ($p<0.01$). Statistically significant differences from baseline (day 1) were observed for IL-6 level ($p=0.02$) from day 3 onwards and for CRP level ($p<0.01$) from day 5 onwards, suggesting that these parameters may serve as predictive markers of early DIC improvement.

In the persistent DIC group (n=3), on the other hand, the median values on days 1, 3, 5, 7, and 9 were respectively as follows: platelet counts, 6.2, 2.3, 1.4, 1.2, and $2.9\times10^4/\mu L$; FDP levels, 58.2, 46.7, 31.7, 35.9, and 76.2 μg/mL; PT-INR levels, 1.3, 1.3, 1.3, 1.3, and 1.5; Fib levels, 192.0, 211.0, 178.0, 178.0, and 174.0 mg/dL; AT III levels, 56.0%, 76.0%, 75.0%, 72.0%, and 59.0%; CRP levels, 5.0, 16.2, 5.4, 7.8, and 6.1 mg/dL; HMGB-1 levels, 7.6, 10.8, 9.7, 6.6, and 12.9 ng/mL; and IL-6 levels, 54.9, 50.3, 31.1, 25.5, and 75.2 pg/mL (Fig. 5). All of these parameters except AT III level showed worsening on day 9, as compared with those on day 1.

3. Comparisons among AT-, rTM-, and AT+rTM-treated groups

DIC score did not differ among the AT-, rTM-, and AT+rTM-treated groups at the start of treatment (day 1) ($p=0.40$), but differed significantly on day 3 ($p<0.01$), day 5 ($p<0.01$), and day 7 ($p=0.01$) (Fig. 6). Patients with a baseline AT III level ≤69% with no improvement in DIC score following 3-day AT medication showed slow improvement subsequent administration of rTM. There were no significant differences in DIC score ($p=0.05$) on day 9, and the findings suggest that rTM is effective for AT-resistant DIC albeit with slow responses to treatment.

4. Comparison between biliary drainage and nondrainage subgroups

Among the 14 patients with AC, the biliary drainage (n=7) and nondrainage (n=7) subgroups were compared. Successful endoscopic biliary drainage was performed in seven patients (ENBD in five and EBS in two patients). Reasons for nondrainage included failure to secure consent in five patients with advanced carcinoma, refusal in one, and technical failure in one. Baseline (day 1) DIC score did not differ significantly between

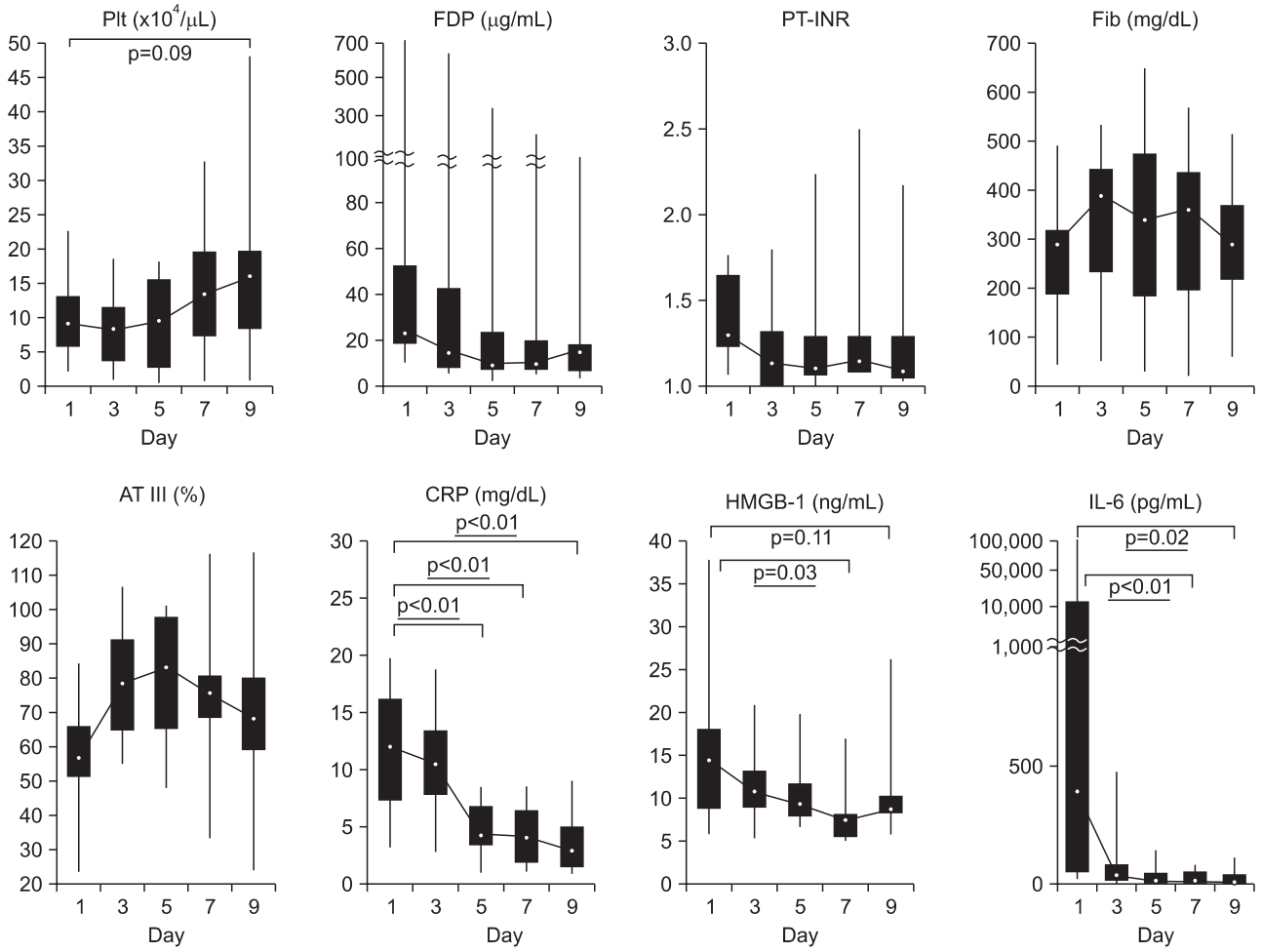

Fig. 3. Time courses of changes in the median values of parameters.
Plt, platelet count; FDP, fibrin/fibrinogen degradation product; PT-INR, prothrombin time-international normalized ratio; Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; HMGB-1, high mobility group box 1; IL-6, interleukin-6.

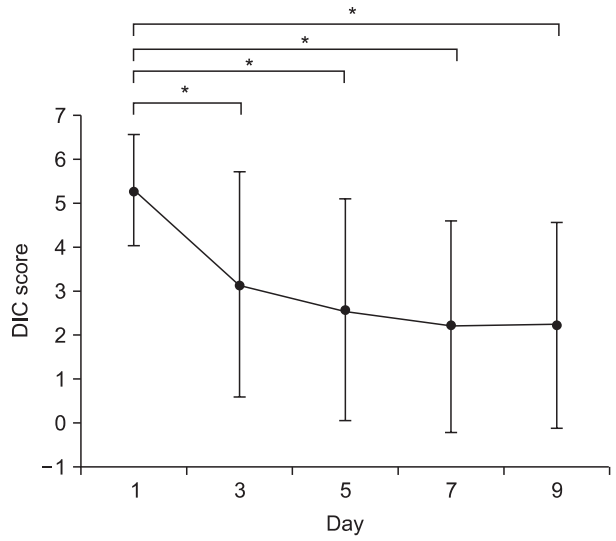

Fig. 4. Time course of changes in the mean values of disseminated intravascular coagulation (DIC) scores.
*p<0.01.

the biliary drainage and nondrainage subgroups (p=0.69), but patients receiving drainage showed a progressive improvement in DIC score, which significantly differed from that of the nondrainage group on day 9 (p=0.03) (Fig. 7). However, in the nondrainage subgroup, mean DIC score showed improvement on day 9 as compared with those on day 1.

5. Adverse events and outcomes

An adverse event occurred in one patient, i.e., bleeding from gastric cancer as a concurrent disease. This event was first observed in the form of tarry stools on day 6 of treatment with rTM, which required a 4-unit packed red cell transfusion, but hemostasis was achieved conservatively by discontinuation of rTM and administration of omeprazole. The outcome on day 28 after the start of treatment was survival in 11 patients and death in three. All three deaths were due to progression of malignant tumors as concurrent diseases.

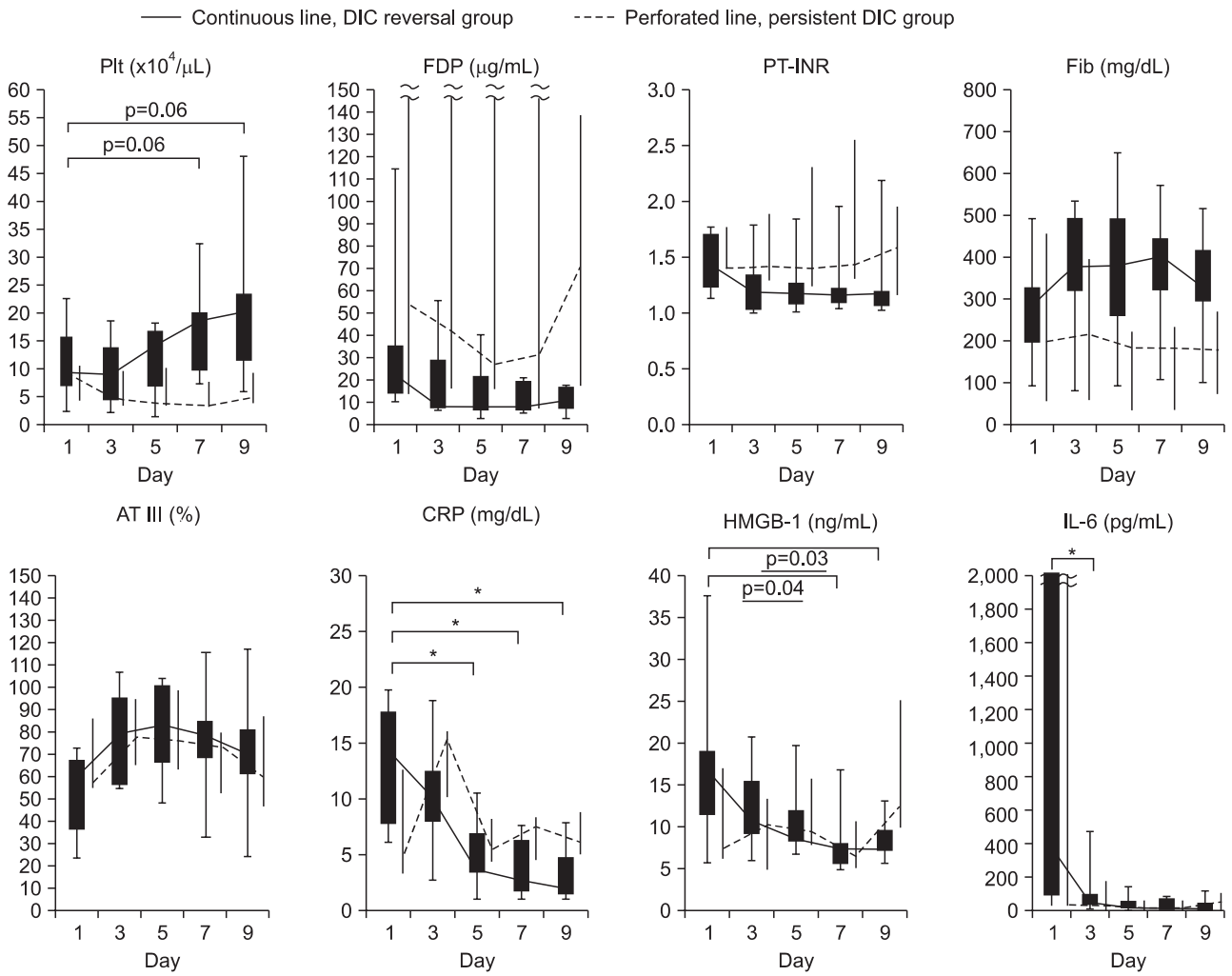

Fig. 5. Comparison of serum parameters between patients with disseminated intravascular coagulation (DIC) reversal and patients with sustained DIC.
Plt, platelet count; FDP, fibrin/fibrinogen degradation product; PT-INR, prothrombin time-international normalized ratio; Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; HMGB-1, high mobility group box 1; IL-6, interleukin-6.
*p<0.01.

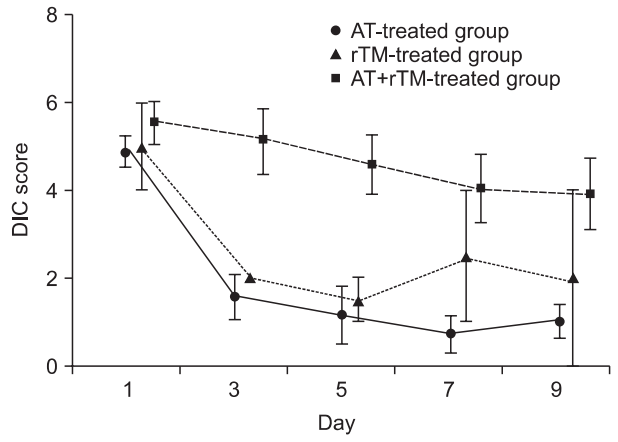

Fig. 6. Comparisons of disseminated intravascular coagulation (DIC) scores among antithrombin (AT)-, TM-, and AT+thrombomodulin (rTM)-treated groups.

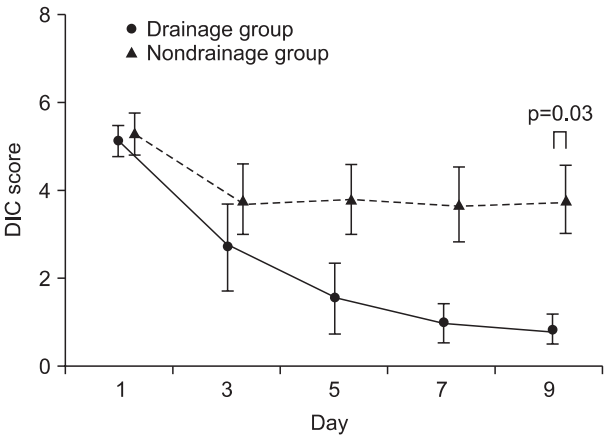

Fig. 7. Comparison of disseminated intravascular coagulation (DIC) scores between the biliary drainage and nondrainage subgroups.

DISCUSSION

The disease state of DIC in AC is of the hypercoagulable-hypofibrinolytic type, and excluding the treatment of the underlying disease, anticoagulants are the drugs mostly recommended in the Japanese Guideline for Treatment of DIC (grade of recommendation, A). Anticoagulant therapy with AT is the most highly recommended treatment (grade of recommendation, B1).[1]

AT is a physiological serine protease inhibitor that controls blood coagulation reactions mainly by inhibiting activated blood coagulation factor X and thrombin. Besides its anticoagulant activity, AT binds to heparin sulfate on vascular endothelial cells and promotes prostaglandin I2 production, thereby stabilizing activated neutrophils, and also binds to syndecan-4 in neutrophils, thereby decreasing the amount of chemokine receptors on the neutrophils. These events suppressing neutrophil chemotaxis produce anti-inflammatory effects.[3,4] In septicemic patients, severity grade reportedly shows an inverse correlation with plasma AT III level.[5] A large-scale clinical trial (KyberSept trial) in patients with severe sepsis showed no improvement of the prognosis with AT.[6] However, analysis of a subgroup of patients with concomitant DIC not treated with heparin among the study patients revealed a significant improvement in the outcome after 28 days as compared with that in a placebo group.[7]

Meanwhile, rTM has been available as a novel therapeutic agent for DIC since May 2008, making Japan the first country in the world to use this drug for DIC. Double-blind randomized clinical trials of rTM in Japan demonstrated its noninferiority to heparin.[8] Hence, a new treatment strategy for DIC is anticipated. The rTM is a drug produced by recombinant DNA technology using an extracellular domain containing the active moiety of rTM, a glycoprotein occurring on vascular endothelial cells, and rTM is a physiological anticoagulation factor that modulates blood coagulation *in vivo*.[9] The rTM activates protein C by reversibly binding to thrombin, and the activated protein C inhibits excessive thrombin production, eventually exerting an anticoagulant effect by suppressing the activation of the blood coagulation system.[10] Furthermore, it has been observed that rTM *per se* produces a direct anti-inflammatory effect, in that the lectin-like domain of rTM adsorbs HMGB-1 and thus exerts an anti-inflammatory effect by suppressing inflammatory cytokine production via stimulation of HMGB-1 lysis by thrombin.[11,12] A retrospective subgroup analysis of data from DIC patients with underlying infections also showed the usefulness of rTM.[13]

However, there is no consensus as yet regarding the use of this novel therapeutic agent, rTM, for DIC. The safety and usefulness of treatments combining AT and other drugs for DIC also remain to be clarified. There have been no reports documenting results of treatment primarily with AT and/or rTM particularly in DIC patients with AC. We therefore devised an original, minimally cumbersome algorithm that corresponds to changes in a patient's clinical status over time, whereby hematologic/blood biochemical data were prospectively obtained 2 days apart, and treatment results based on the algorithm were examined. For the diagnosis of DIC, there are three sets of diagnostic criteria: the Ministry of Heath, Labour and Welfare Diagnostic Criteria for DIC, the Diagnostic Criteria for Acute-Phase DIC, and the International Seciety on Thrombosis and Heamostasis Diagnostic Criteria. We employed the Diagnostic Criteria for Acute-Phase DIC, which is considered to be highly sensitive for DIC caused by infections and superior for early diagnosis although low in specificity.[2] With this treatment strategy, no heparin preparation was used because the anti-inflammatory effect of AT was reportedly inhibited by the concomitant use of heparin and because there was concern about adverse hemorrhagic reactions during treatment with multiple anticoagulants including rTM.[3] Since it is not covered by insurance if the plasma level of AT III is more than 70% in Japan, patients with baseline plasma AT III levels $\leq$69% were treated with AT, and those with baseline plasma AT III levels $\geq$70% were administered rTM. The patients were assessed again on day 3 of treatment and those exhibiting no improvement on AT therapy were administered rTM concomitantly thereafter. By day 7, about 80% of the patients had attained DIC reversal, suggesting the usefulness of this algorithm for treating DIC.

As an adverse event, hemostasis was achieved conservatively by discontinuation of rTM and administration of omeprazole. No other drug-related adverse events were observed, indicating the safety of this strategy. Nevertheless, the hemorrhage developed on day 6 of treatment with rTM in this case. As the duration of rTM treatment was specified as being up to 6 days in a Japanese phase III clinical trial of rTM,[8] it will be necessary to examine the safety of rTM administration for a longer period by assessing more cases.

Comparisons of responses among the three treatment groups revealed that the AT+rTM-treated group, in which rTM was combined with AT because patients showed no improvement in DIC score on day 3 of AT therapy, still showed a slower improvement in DIC score than the other two treatment groups, suggesting that these patients might be treatment-resistant. However, the difference between the DIC score of this combined regimen group and that of the other two groups tended to diminish progressively, suggesting the usefulness of rTM for treating AT-resistant DIC. It would be important to determine the optimal timing of instituting concomitant AT and rTM. In fact, the decision was made on day 3 or 4 of AT therapy in a study reported by Eguchi,[14] who stated that rTM is useful for AT-resistant DIC. However, as our results, it may be better to administer rTM and AT simultaneously from day 1 if the plasma level of AT III is less than 70%. Further investigation is necessary concerning the timing and dose among others in the AT+rTM regimen.

In this study, predictive markers of early DIC improvement

were examined. The results showed significant differences in IL-6 level and CRP level within the first 5 days of treatment between the reversed and persistent DIC groups. This finding suggests that these parameters might serve as predictive markers of early DIC improvement. With regard to prognostic markers of DIC exacerbation and the difference between the reversed and persistent DIC groups, on the other hand, evaluation was difficult because there were only three patients in the persistent DIC group, yet all the parameters other than AT III level worsened in this group. We also examined HMGB-1 level, which was first reported by Wang *et al*.[15] and has been drawing attention as a lethal mediator. A significant improvement in HMGB-1 level was noted in the DIC reversal group on day 7, as compared with the baseline value; whereas in the persistent DIC group, this parameter tended to worsen. Therefore, although this parameter cannot reliably be regarded as a predictive marker of an early therapeutic response, it is noteworthy that the worsening of HMGB-1 level was evident despite the improved or unchanged DIC score in the three patients who died from cancer within 28 days. Hence, the worsening of HMGB-1 level might be of value as an indicator of not only the exacerbation of DIC but also the worsening of the general condition.

Comparison between biliary drainage and those without, it revealed a significantly greater improvement in the drainage subgroup than the nondrainage subgroup. This implies that the treatment of cholangitis should be undertaken as aggressively as possible. In this study, in which a considerable proportion of patients had advanced carcinoma and not a few were reluctant to give consent for the drainage procedure, DIC score still tended to improve even among patients in the nondrainage subgroup. Althouh the biliary drainage as the treatment of underlying disease is the most important, it seems that this algorithm is effective especially with the cases who cannot be performed drainage.

Finally, it is necessary to consider that the results of the present manuscript contain biases such as the therapeutic efficacy of drugs, other than AT and rTM, that were used concomitantly, and that of biliary drainage. However, we believe that these observations will contribute to patient management in clinical settings, because this is the first part of a collective report on clinical experiences in using AT and rTM for the treatment of DIC complicating AC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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