Systemic inflammatory response syndrome strongly affects the prognosis of patients with fulminant hepatitis B

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Background. Hepatitis B virus infection is the most frequent cause of fulminant hepatic failure. Recently, systemic inflammatory response syndrome has been reported to be important in patients with fulminant hepatic failure. However, prognostic factors for fulminant hepatitis B have not been fully examined. In this study, we analyzed prognostic factors for fulminant hepatitis B in order to accurately identify patients with fatal outcomes.

Methods. Of 110 consecutive patients with fulminant hepatic failure, 36 (33%) were diagnosed with fulminant hepatitis B. Five of the 36 patients received liver transplants, and we analyzed prognostic factors associated with fatal outcomes in the other 31 patients, who consisted of 15 men and 16 women with a median age of 45 (range, 20–74) years.

Results. Eleven patients (35%) survived without liver transplantation, and the remaining 20 (65%) died. Nonsurvivors were older and had a higher prevalence ratio of systemic inflammatory response syndrome than survivors. Treatments were similar between survivors and nonsurvivors. Using a multivariate Cox proportional hazard model, age (>45 years), systemic inflammatory response syndrome, and ratio of total to direct bilirubin (>2.0) were associated with fatal outcomes. In particular, 1-week and overall survival rates of patients with systemic inflammatory response syndrome at the time of diagnosis were 39% and 8%, respectively, while those of patients without systemic inflammatory response syndrome were 94% and 56%, respectively.

Conclusions. Systemic inflammatory response syndrome strongly affects the short-term prognosis of patients with fulminant hepatitis B, and patients with systemic inflammatory response syndrome might need urgent liver transplantation.

Key words: fulminant hepatitis B, systemic inflammatory response syndrome, ratio of total to direct bilirubin

Introduction

Worldwide, hepatitis B virus infection is the most frequent cause of fulminant hepatic failure. It has been reported that fulminant hepatitis B occurs in approximately 1% of patients with acute disease and carries a mortality rate of up to 80%.1–3 To predict the prognosis of patients with fulminant hepatic failure, various prognostic factors such as cause (viral hepatitis, acetaminophen overdose, etc), prothrombin time, hepatic coma grade, and age have previously been proposed.2 Recently, systemic inflammatory response syndrome has been reported to be a new prognostic factor for patients with fulminant hepatic failure and to be related to the worsening of hepatic coma.4–6 Furthermore, a number of prognostic systems for fulminant hepatic failure have been proposed,2,6–8 and the King’s College criteria have been widely accepted.2,9 However, the King’s College criteria have been reported to have a lower predictive accuracy than shown in the original study.9

In hepatitis B virus infection, it has been reported that precore mutation, core promoter mutation, and hepatitis B virus genotype are associated with the development of fulminant hepatitis.10–13 On the other hand, Takahashi et al.7 reported that some factors, such as the serum level of total bilirubin, ratio of total to direct bilirubin, age, white blood cell count, and prothrombin time are associated with the outcomes of patients with fulminant hepatitis B. However, prognostic factors for patients with fulminant hepatitis B have not been fully examined.

According to a recent study in the United States, only two-thirds of the patients who are candidates for liver transplantation can receive that treatment.3 The remaining patients die due to the rapid development of cerebral edema or multiple organ failure before they can receive liver transplantation.3 If we are able to accurately identify patients with a fatal outcome,
liver transplantation can be performed promptly, and the number of unnecessary transplants for patients who will survive without liver transplantation can be reduced. In this study, we analyzed the prognostic factors for patients with fulminant hepatitis B in order to accurately identify patients with a fatal outcome.

Patients and methods

Patients

A hundred and ten consecutive patients with fulminant hepatic failure, 45 men and 65 women with a median age of 48 (range, 16–81) years, admitted to Okayama University Hospital or 11 affiliated hospitals with a liver transplantation program for fulminant hepatic failure, which started in 1998, between January 1990 and March 2005, were enrolled in the study.

Diagnosis of fulminant hepatic failure

Patients with fulminant hepatic failure were those in whom encephalopathy of coma grade greater than II occurs within 8 weeks from the first symptoms of illness, and who have a prothrombin time of less than 40% the normal value and no previous chronic or alcoholic liver diseases.14 Hepatic coma was graded on the standard scale of I to IV. Patients whose ultrasonography or computed tomography showed the features of chronic liver disease (splenomegaly, atrophy of the right lobe with enlargement of the left lobe, and varices or collaterals) were excluded from this study.

Cause of fulminant hepatic failure

A diagnosis of fulminant hepatitis A, B, or C was made based on the presence of the IgM anti-hepatitis A virus antibody, IgM anti-hepatitis B virus core antibody, or the hepatitis B surface antigen, and hepatitis C virus-RNA identifiable by nested reverse transcription polymerase chain reaction, respectively. A diagnosis of fulminant-type autoimmune hepatitis was made based on the presence of anti-nuclear or anti-smooth muscle antibody and the criteria defined by the International Autoimmune Hepatitis Group.15 A diagnosis of drug-related fulminant hepatic failure, acute fatty liver of pregnancy, or ischemic liver injury was made based on their distinctive clinical courses. A diagnosis of indeterminate fulminant hepatic failure was established when the IgM anti-hepatitis A virus antibody, IgM anti-hepatitis B virus core antibody, hepatitis B surface antigen, hepatitis C virus-RNA, and anti-nuclear and anti-smooth muscle antibody were negative, and no obvious cause such as drug, acute fatty liver of pregnancy, ischemic hepatitis, Wilson’s disease, malignant infiltration, cytomegalovirus, Epstein-Barr virus, or herpes simplex was present.

Diagnosis of systemic inflammatory response syndrome

Systemic inflammatory response syndrome was defined according to the criteria of the Consensus Conference on Sepsis and Multiple Organ Failure:16 a temperature >38°C or <36°C, heart rate >90 beats per minute, tachypnea >20 breaths per minute or PaCO₂ <4.3 kPa, white blood cell count >12 × 10⁹/mm³ or <4 × 10⁹/mm³, or the presence of immature neutrophils >10%. Systemic inflammatory response syndrome was diagnosed by the presence of two or more components.

Treatment

All patients were admitted to the intensive care unit and received supportive care by the monitoring of clinical, biochemical, and hemodynamic parameters. Patients received lamivudine treatment, pulse steroid treatment, administration of protease inhibitor, plasma exchange, or hemodiafiltration. As antiviral therapy, 100–200 mg/day of lamivudine was administered. Pulse steroid treatment was performed with 500–1000 mg/day of methylprednisolone for 3 days in order to suppress the activity of liver injury. As a protease inhibitor, 1000–2000 mg/day of gabexate mesilate or 100–200 mg/day of nafamostat mesilate was administered to prevent the development of disseminated intravascular coagulation. Plasma exchange was performed three to five times during the initial 7–10 days in order to remove unfavorable substances such as protein-binding agents, endotoxins, and immune complexes from the plasma, and to supplement coagulation factors. The duration and volume of plasma exchange was 5–6 h and 3.2–4.8 l, respectively. Hemodiafiltration was also performed continuously or over 3 to 4 h to enhance the removal of the causative medium-sized molecules of hepatic coma or hepatic failure and to maintain the acid–base balance. The indications at the time of apheresis performance were the following: (1) patients with coagulopathy were indicated for plasma exchange; (2) patients with the central nerve disorder, including hepatic encephalopathy, were indicated for plasma exchange only or plasma exchange combined with hemodiafiltration; and (3) patients with renal failure caused by fulminant hepatic failure were indicated for hemodiafiltration. When the circulation state was unstable, continuous hemodiafiltration was performed.

Liver transplantation was performed in patients based on the criteria established in 1996 by the Acute Liver Failure Study Group of Japan.14 These criteria are simi-