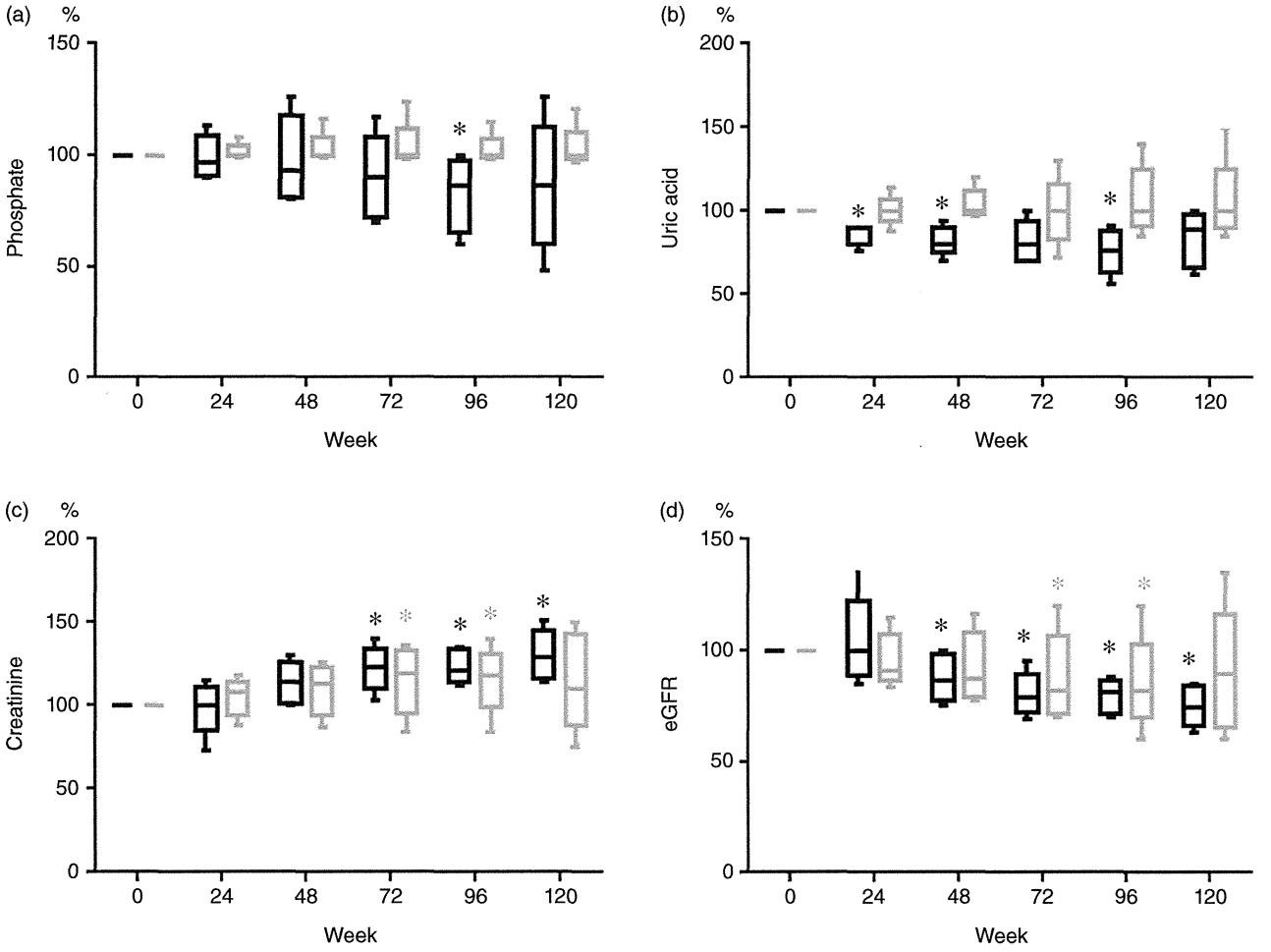
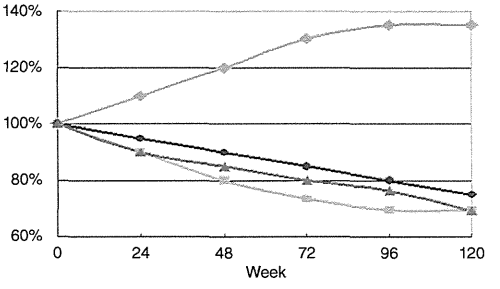


Figure 3 Changes in parameters in relation to period of adefovir dipivoxil (ADF) treatment. (a) Phosphate. (b) Uric acid. (c) Creatinine. (d) Estimated glomerular filtration rate (eGFR). $^*P < 0.05$ as compared with beginning of treatment. ☐, group A; ☐, group B.

the present data is not enough to conclude that decrease of uric acid and eGFR is an earlier event. It is needed to confirm whether it is right or not by analyzing large number of subjects or by another validation study. In group B in the present study, decrease of eGFR was found but decrease of phosphate was not found. It should be noted that some patients in group B showed elevated Cr or decreased eGFR. Careful follow-up examinations are needed for such patients to check for emergence of hypophosphatemia in the near future. In addition, kidney stones or urinary crystals with occult hematuria were noted in a considerable number of our patients, which was considered to be caused by increases in various substances in urine caused by a disturbance of reabsorption in the proximal tubules. Screening of urine in patients treated with ADF may be also important.



Creatinine (mg/dl)	0.99	1.09	1.19	1.29	1.34	1.34
eGFR (ml/min/1.73 m^2)	66.2	59.8	53.0	48.6	46.1	46.1
Phosphate (mg/dl)	3.2	3	2.9	2.7	2.6	2.2
Uric acid (mg/dl)	4.2	6.5	5.8	5.7	5.5	5.0

Figure 4 Changes in phosphate, creatinine, estimated glomerular filtration rate (eGFR) and uric acid in group A. Percentages obtained at the beginning of treatment were considered to be 100% and changes in those values are shown. —, creatinine; —, eGFR; —, phosphate; —, uric acid.

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In conclusion, hypophosphatemia occurred in 35% of the patients under long-term treatment with ADF. Although it was not possible to predict the decrease in phosphate before ADF therapy, decreases in uric acid and eGFR may be the early events relating to low phosphatemia. Additional studies are needed to clarify whether these phenomena precede low phosphatemia.

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症例報告

悪性リンパ腫に対してRituximabを使用しHBV再増殖による重症肝炎を来した3例
－免疫抑制・化学療法にともなうB型肝炎対策ガイドラインの検証－

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Three cases of serious hepatitis due to the enhancement of hepatitis B virus replication induced by treatment with rituximab
-Verification of the Japanese guideline for prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection-

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Summary

We had experienced three cases of serious hepatitis due to the enhancement of hepatitis B virus (HBV) replication induced by rituximab treatment (anti-CD20 monoclonal antibody) for malignant lymphoma. Two cases were HBV reactivation from patients with HBs antigen negative (de novo HBV hepatitis), and one case was the enhancement of HBV from a patient with HBs antigen positive. Among them, two cases were died. However, all of the patients were treated with nucleotide analogues. In 2009, the Japanese guideline for prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection was presented. Two of our cases were treated in conformity to the guideline, however, we could not prevent serious hepatitis with HBV enhancement. The guideline should be discussed in a timely manner to establish a safer treatment for patients taking rituximab who are infected with HBV.

Key Words : hepatitis B virus, de novo HBV hepatitis, rituximab

はじめに

Rituximabなど分子標的薬の投与により，宿主免疫が強力に抑制されB型肝炎ウイルス（HBV）による重症肝炎を来し，一部の症例では致死的な経過をたどることが報告されている[1)~3)]。

本邦では2009年に厚生労働省研究班による免疫抑制・化学療法にともなうB型肝炎対策ガイドラインが発表された[4)]。著者らはHBV既往感染およびキャリア例である悪性リンパ腫の患者で，rituximab投与によりHBVが再増殖し重症肝炎に至った症例を3例経験した。治療ガイドラインと比較検討し報告する。

2012年10月25日受付　2013年1月24日採用

症　例

症例1

患　者：59歳　男性
主　訴：黄疸

既往歴：19歳時　右下肢骨腫瘍手術

家族歴：父　膵癌

現病歴：悪性リンパ腫再発に対し，2004年7月よりrituximab＋etoposide施行(rituximab 3, 600 mg，etoposide 1, 400 mg，総投与量)。6コース目施行中の9月より肝機能増悪あり。その際HBs抗原陽性，HBV-DNA 8.7 LGE/ml (TMA法) と，HBV再活性化がみられた。HBs抗原陽転後，lamivudine 100 mg/day投与したが肝機能は増悪し，当科に紹介され入院した。

入院時現症：体温37.4℃，血圧112/62 mmHg，脈拍58回/分・整，意識清明，皮膚黄染，眼球結膜黄疸あり，羽ばたき振戦なし。

入院時検査所見：総ビリルビンの上昇，AST・ALTの上昇が著明で，PT35.8%と低下あり。肝予備能の低下がみられた (Table 1)。B型肝炎ウイルス (HBV) マーカーは，HBs抗原陽性，HBV-DNA陽性，HBe抗原陰性，HBe抗体陰性，HBs抗体陰性であった。

入院後経過：入院前より内服していたlamivudine 100 mg/dayの投与を継続し，入院時よりステロイドパルス療法 (methylprednisolone 1, 000 mg/day 3日間) を開始した。HBV-DNA量は減少傾向であったが，入院後第9病日に39℃の発熱およびⅢ度の肝性脳症を合併し，遅発性肝不全 (late onset hepatic failure; LOHF) と診断した。その後も治療を継続したが肝不全が進行し，入院後第47病日に死亡した (Fig. 1)。

Table 1. Laboratory data on admission of 3 cases

	Case 1	Case 2	Case 3
Hematology			
Hemoglobin	10.3 g/dl	14.7 g/dl	13.4 g/dl
RBC	332 ×10⁴/mm³	446 ×10⁴/mm³	396 ×10⁴/mm³
Hematocrit	28.8 %	40.4 %	38.0 %
WBC	3500 /mm³	11400 /mm³	4300 /mm³
stab	44 %	25 %	
seg	31 %	62 %	62 %
lymphocyte	6.0 %	5.0 %	34.1 %
CD3	Not done	79 %	72 %
CD19	0%	0 %	15 %
Platelet	8.1 ×10⁴/mm³	12.8 ×10⁴/mm³	15.3 ×10⁴/mm³
Coagulation			
Prothrombin time	31.7 %	38.9 %	76.8 %
Hepaplastin test	20.8 %	28.0 %	
APTT	34.7 sec	47.0 sec	
Blood chemistry			
T. Bilirubin	26.0 mg/dl	23.4 mg/dl	1.0 mg/dl
D. Bilirubin	17.8 mg/dl	15.6 mg/dl	0.2 mg/dl
AST	519 IU/l	85 IU/l	668 IU/l
ALT	308 IU/l	447 IU/l	830 IU/l
γ-GTP	149 IU/l	80 IU/l	86 IU/l
Ferritin	13387 μg/ml	2649 μg/ml	1149 μg/ml
NH_3	26 μg/dl	101 μg/dl	44 μg/dl
Soluble IL-2 receptor	1665 U/ml	1284 U/ml	320 U/ml
IgG	772 mg/dl	712 mg/dl	872 mg/dl
Hepatitis virus markers			
HBs Ag	(+) 11671 IU/ml	(+) 4121 IU/ml	(+) 21480 IU/ml
HBe Ag	(-)	(-)	(-)
HBe Ab	(-)	(+)	(-)
Anti-HBc (× 1)	(+)	(-)	(+)
(× 200)	(-)	(-)	(-)
HBs Ab	(-)	(-)	(-)
HBV-DNA	(amplicore) 6.9 LogC/ml	(amplicore) 4.6 LogC/ml	(real time PCR) 7.6 LogC/ml
HBV precore mutation	(-)	(-)	(-)
HBV genotype	C	C	B
HBV YMDD lamivudine mutation	(-)	(-)	(-)
Anti-HCV	(-)	(-)	(-)
HCV-RNA	(-)	(-)	(-)

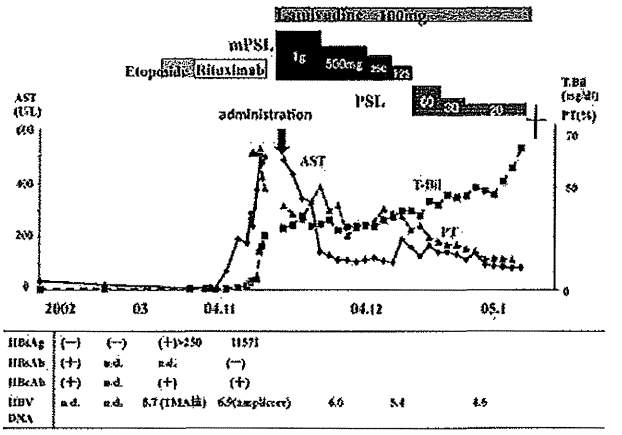

Fig. 1. Clinical course and hepatitis B virus (HBV) markers of case 1.
Before the treatment of rituximab, HBs antigen was negative, HBs antibody and HBc antibody were positive. However, after the treatment of rituximab, those antigen and antibodies were converted. The liver failure was progressed nevertheless of the treatment with lamivudine, and the patient had died at 47 days after admission.

症例2

患　者：47歳　男性

主　訴：倦怠感

既往歴：20歳時　黄疸出現（詳細不明）

家族歴：母，弟　直腸癌

現病歴：1997年より1999年にかけて悪性リンパ腫に対して近医でhigh dose CHOP療法 (cyclophosphamide 2, 200 mg，vincristine 2 mg，adriacin 50 mg，prednisolone 100 mg，総投与量) を計7コース施行。2004年5月悪性リンパ腫再発に対してrituximab投与を開始した。2005年9月の血液検査でHBs抗原陽性，HBV-DNA 4.4 LogC/mlでHBVキャリアであったため9月よりlamivudine 100 mg/day投与開始し以後投与継続した。その後11月にrituximabを再投与したところ，2006年2月14日ALT上昇，HBV-DNA量の増加(8.7 LogC/ml)あり，

HBVによる肝障害と診断しadefovir　10 mg/dayを追加した。さらにステロイドパルス療法(methylprednisolone 1,000 mg/day 3日間）を開始したが，肝機能増悪し，当科に紹介され入院した。

入院時現症：体温36.7℃，血圧100/54 mmHg，脈拍87回/分・整，意識清明，皮膚黄染，眼球結膜黄疸あり，羽ばたき振戦なし

入院時検査所見：PT 38.9%と低下し，総ビリルビンは23.4 mg/dlと高値であった（Table 1）。HBV-DNA 4.6 LogC/ml，HBe抗原陰性，HBe抗体陽性であった。

入院後経過：入院後もlamivudine，adefovir，ステロイド投与を継続した。HBV-DNA　3.8 LogC/mlと減少したが，PTの改善なく，総ビリルビン値も高値が持続した。治療継続にもかかわらず肝予備能は回復することなく徐々に低下し，肝不全に肺炎を合併して第16病日に死亡した（Fig. 2）。

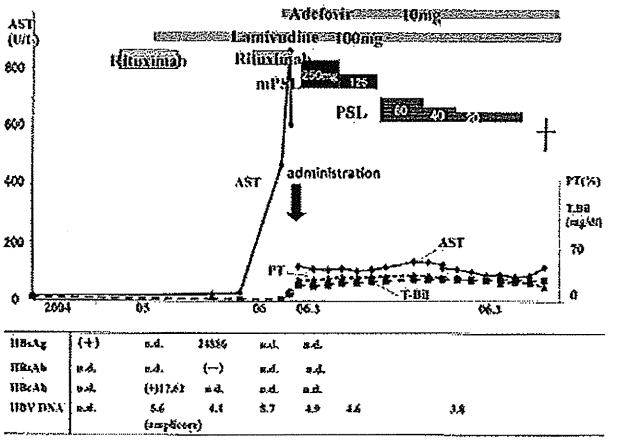

Fig. 2. Clinical course and hepatitis B virus (HBV) markers of case 2.
The patient was HBV carrier, and he was treated with lamivudine before the second course of rituximab treatment. However, after the treatment with rituximab, HBV-DNA was dramatically increased, and induced liver failure. The combined therapy with lamivudine and adefovir could not improve the liver function, and the patient had died at 16 days after admission.

症例3

患　者：59歳　男性

主　訴：黄疸

既往歴：特記事項なし

家族歴：母　胃癌

現病歴：悪性リンパ腫に対して2010年3月R-CHOP療法（rituximab 660 mg，cyclophosphamide 1,250 mg，adriacin 86 mg，vincristine 2 mg，prednisone 100 mg，総投与量）を開始。HBc抗体陽性であったため2010年5月よりlamivudine　100 mg/dayを投与し，R-CHOP療法終了1年後まで投与継続した。その後，定期的に経過観察していた。2012年2月29日のHBV-DNA<2.1 LogC/mlと陽転し，同年5月30日にHBs抗原も陽転，HBV-DNA　8.4 LogC/mlと増加したため当科を紹介受診した。Entecavir 1 mg/day内服を開始したが，6月25日の採血でAST，ALTの上昇がみられ当科に入院した。

入院時現症：体温36.2℃，血圧114/60 mmHg，脈拍72回/分・整，意識清明，皮膚黄染，眼球結膜黄疸あり，羽ばたき振戦なし

入院時検査所見：PT 76.8%と軽度低下。ビリルビン，ALTの上昇あり，肝機能障害がみられた（Table 1）。HBs抗原陽性，HBV-DNA　7.6 LogC/ml，HBe抗原および抗体はともに陰性であった。

入院後経過：入院後entecavir　1 mg/day内服を継続し，HBV-DNAは低下傾向であったが，総ビリルビンの上昇，PTの低下傾向が持続し，入院後第11病日よりステロイドパルス療法（methylprednisolone　1,000 mg/day 3日間，以後漸減）を開始した。その後，総ビリルビン値の低下，PTの改善がみられ，HBV-DNA量は徐々に低下し，ステロイド中止後も肝機能増悪がないため，第53病日に退院した（Fig. 3）。

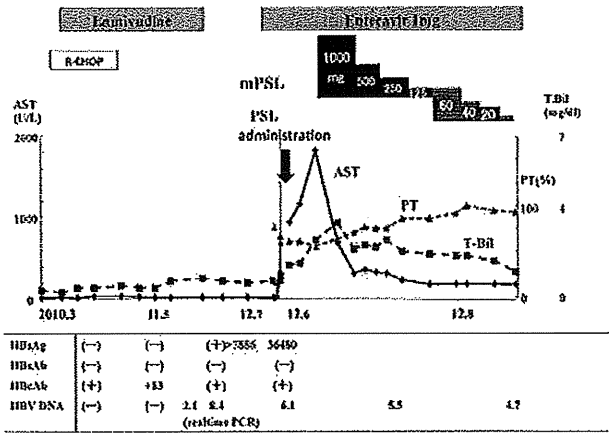

Fig. 3. Clinical course and hepatitis B virus (HBV) markers of case 3.
Before the treatment of rituximab, only the HBc antibody was positive. Moreover, the patient was treated with lamivudine at the time of treatment with rituximab, and continued lamivudine administration one year after the treatment with rituximab. However, de novo HBV hepatitis had occurred, and the patient needed the treatment of entecavir with steroids.

考 察

HBVは肝細胞に感染後，核内にcccDNA（covalently closed circular DNA）を形成して持続感染し続けることが知られている[5)-8)]。免疫抑制療法や化学療法による免疫抑制により，HBV cccDNAからmRNAの転写を介してHBVが再増殖する場合がある[5)]。HBV再増殖のなかで，特にHBs抗原陰性例がHBs陽転する事象をHBV再活性化という。症例1と3は再活性化である。Yeoらは193例のHBs抗原陽性悪性リンパ腫症例に対する全身化学療法で，24%の症例がHBV再増殖による肝炎を発症したと報告しており[9)]，HuiらはHBs抗原陰性悪性リンパ腫244例に全身化学療法を施行して，HBV再活性化による肝炎を8例（3.3%）に認め，8例全例でHBc抗体あるいはHBs抗体陽性であったと報告している[10)]。近年，特にrituximabに起因するB型重症肝炎が臨床上大きな問題になっている。特にHBs抗体陰性例はリスクが高い[3)]。

そのため，HBVキャリアやHBc抗体あるいはHBs抗体陽性例が悪性リンパ腫を発症し，rituximabを投与する場合には，HBVに対する核酸アナログ投与の必要性を検討するべきである。本邦では2009年に「厚生労働省研究班による免疫抑制・化学療法にともなうB型肝炎対策ガイドライン」[4)]が提示された。HBs抗原陽性例に対する免疫抑制・化学療法時には核酸アナログの予防投与を行い，HBs抗原陰性でもHBc抗体あるいはHBs抗体陽性患者には，月1回，化学療法中および化学療法終了後に少なくとも1年間のHBV-DNAモニタリングを行うこと。HBV-DNAが陽転化した時点で速やかな核酸アナログの投与開始が必要であることが示されている。

提示した3症例の概要を表に示す（Table 2）。症例1はガイドライン提示前の症例であり，当時HBs抗体陽性症例からのHBV再活性化の報告もなく，治療中および治療後の定期的なHBV-DNAのモニタリングが行われていなかった。そのため，核酸アナログ投与が遅延したことが救命できなかった要因と考えられる。rituximab使用前にHBs抗体陽性であってもHBV再活性化を来す危険性があることを，治療を施行する医師は充分認識する必要がある[11)]。

症例2はHBVキャリアの患者で，HBs抗原陽性であったため2クール目のrituximab開始前，ALT正常の状態からlamivudineの予防投与をおこなったにもかかわらず，HBV-DNAが再増殖し，死亡した。本症例で

Table 2. Clinical features of 3 cases with serious hepatitis B after administration of rituximab

	投与前HBV検査				肝不全治療前のPeak値		核酸アナログ投与時期	転帰	HBV再活性化の原因
	HBs Ag	HBc Ab	HBV Ab	-DNA	T. Bil	PT			
症例1 59歳 男 2004年	(-)	(+)	(+)	未検	26.4	35.8	ALT上昇後1ヶ月 Rituximab投与開始後3ヶ月	死亡	HBVモニターなし 核酸アナログ治療開始遅れ
症例2 47歳 男 2006年	(+)	(-)	(+)	5.6	23.4	38.9	ALT上昇前 Rituximab投与開始後4ヶ月	死亡	投与開始後4ヶ月でのラミブジン予防投与でも重症化 HBVモニター不完全
症例3 59歳 男 2012年	(-)	(-)	(+)	(-)	3.7	64.0	ALT上昇前 Rituximab投与開始後2ヶ月	救命	12ヶ月ラミブジン治療後に発症 HBVモニター不完全 12ヶ月以上の核酸アナログ投与の必要示唆

※ガイドライン作成報告 2009年　　投与: rituximab投与

核酸アナログを予防投与したにもかかわらず，HBV再増殖を来した理由として，lamivudine耐性株の出現について調べたところ，YIDD，YVDDの耐性変異は検出されなかった。また，患者がlamivudine内服を忘れていた可能性も考え，来院時のlamivudineの血中濃度を測定したが，有効血中濃度以上に保たれており，服薬忘れがHBV増殖の原因ではないと考えられた。

本症例もガイドライン提示前の症例であり，厳密には1クール目のrituximab開始前にlamivudineの予防投与が必要であったと考えられる。しかし，少なくとも1クール目ではHBV-DNAの上昇はみられていない。2クール目の治療前にはガイドラインに沿う形でlamivudineの投与されていたにもかかわらず，HBV再増殖による重症肝炎を発症し，死亡した。このことは，HBVキャリアの場合たとえガイドラインに沿って，核酸アナログを予防投与してもHBV再増殖による重症肝炎，肝不全を回避できない症例があることを示している。予防投与をrituximab治療前のどの時期に開始するか，再検証する必要がある。本症例において肝機能増悪前のHBV-DNA量は4.4 LogC/mlと比較的低値である。Lamivudine投与をより早く先行してHBV-DNAをさらに低下させた後にrituximab投与を行えば，HBV再増殖を予防できた可能性は否定できない。安全なRituximab治療のために，核酸アナログでどの程度までHBV-DNAを下げる必要があるのか，今後さらに症例を蓄積して検討する必要がある。

症例3は最近の症例で，R-CHOP療法開始後，HBs抗原陰性であったが念のためlamivudineを予防投与されていた。ガイドラインに沿ってR-CHOP療法終了12カ月後までlamivudine投与を継続したが，HBs抗原陰

性が持続していたため投与を中止。その後，HBVの再活性化を来した[12]。LauraらはHBs抗原陰性，HBs抗体陽性，HBc抗体陰性の悪性リンパ腫患者に対してrituximab投与後lamivudine投与を12ヶ月継続したが，本症例と同様にHBV再活性化を来した症例を報告している[13]。本症例と報告例はともに，rituximab投与時の核酸アナログ予防投与は必須ではないのか，また核酸アナログは治療終了後12ヶ月の使用で大丈夫なのか，ガイドラインの再考する必要に迫られる症例と考えられる。一方で本症例と報告例はいずれも，lamivudine中断後に月1回の定期的なHBV-DNAのモニターがされておらず，治療開始が遅れたことが肝機能増悪に関わっていた。核酸アナログの使用および中止については，肝臓専門医の専門知識と経験を要すると考えられる。

今後rituximabの適応拡大と使用頻度の増加により，HBVによる重症肝炎例が増加すると考えられる。本報告では，悪性リンパ腫に対してrituximabを投与し，HBV再活性化あるいは再増殖による重症肝炎を発症した3例について考察した。今後さらに症例を蓄積し，免疫抑制・化学療法にともなうB型肝炎対策ガイドラインについて，より安全な基準を求めて検証していく必要があると考えられる。

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Short Communication

Lipid profile is associated with the incidence of cognitive dysfunction in viral cirrhotic patients: A data-mining analysis

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Aim: Cognitive dysfunction (CD) is frequently observed in cirrhotic patients. However, the biochemical profiles associated with CD remain unclear. We investigated the biochemical profiles associated with the incidence of CD in cirrhotic patients by using multivariate analyses, including a decision-tree algorithm.

Methods: In this study, 27 viral cirrhotic patients were enrolled. All subjects underwent neuropsychiatric tests; two or more abnormal results were defined as CD. A logistic regression model was used for multivariate stepwise analysis. A decision-tree algorithm was constructed, and the categorical differences based on the decision-tree model were analyzed by χ^2-tests.

Results: Multivariate stepwise analysis showed the levels of total bilirubin, triglycerides and free fatty acids (FFA) as independent bioparameters associated with the incidence of CD in cirrhotic patients. The decision-tree algorithm showed that among patients with FFA of 514 mEq/L or more, 77.8% had CD. Meanwhile, among patients with FFA of less than 514 mEq/L and triglycerides of 106 mg/dL or more, 20.0% had CD. The sensitivity, specificity and accuracy for the incidence of CD using the lipid profile (FFA >514 mEq/L or triglycerides <106 mg/dL) were 85.7% (12/14), 61.5% (8/13) and 74.1% (20/27), respectively.

Conclusion: The levels of total bilirubin, FFA and triglycerides are independently associated with the incidence of CD in cirrhotic patients. In addition, a decision-tree algorithm revealed that FFA of more than 514 mEq/L or triglycerides of less than 106 mg/dL is a profile associated with the incidence of CD. Thus, this lipid profile could be a possible screening bioparameter for CD in cirrhotic patients.

Key words: decision-tree algorithm, fatty acid, minimal hepatic encephalopathy, neuropsychiatric test

INTRODUCTION

CIRRHOSIS IS FREQUENTLY accompanied by various complications, including esophageal varices and hepatocellular carcinoma.[1,2] Cognitive dysfunction (CD) is another frequent complication in patients with chronic liver disease and is known as minimal hepatic encephalopathy or subclinical hepatic encephalopathy.[3,4] CD predicts the development of hepatic encephalopathy and poor prognosis.[5,6] Moreover, CD itself is associated with impaired health-related quality of life[7–9] and serious social issues such as falls and motor vehicle accidents.[10–16] Therefore, CD is one of the critical complications of chronic liver disease.

Because bacterial overgrowth in the intestine and delayed gastrointestinal transit time are associated with the development of CD,[17] ammonia and pro-inflammatory cytokines derived from enteric bacterial flora are thought to be pathogenic factors of CD. In fact, treatment with gut-specific agents such as lactulose and rifaximin can improve CD in cirrhotic patients.[18–22]

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However, CD is not always correlated with the severity of liver disease, blood levels of ammonia or inflammation.[6] CD can also be caused by malnutrition, cerebrovascular disease secondary to diabetes mellitus and psychoactive agents.[4,12,23,24] These previous reports suggest that complicated interactions between various factors underlie the development of CD in cirrhotic patients.

Data-mining analysis is a set of statistical techniques used to reveal complex interactions within a dataset.[25,26] A decision-tree algorithm is an exploratory data-mining analysis technique that is a series of rules for classification by identifying priorities.[26] This is a quantitative systematic approach that allows clinicians to maximize the net benefit to patients.[27] Decision-tree algorithms are now clinically applied to predict the following issues: response to interferon treatment of hepatitis C virus (HCV);[28] severity of hepatic fibrosis;[29] progression of hepatocellular carcinoma;[29] safety of hepatic resection;[30] outcome of patients with acute liver failure;[31] and dietary factors for normalizing serum alanine aminotransferase levels in patients with HCV infection.[26]

The aim of this study is to investigate the profiles associated with the incidence of CD by using multivariate analyses, including the decision-tree algorithm in cirrhotic patients.

METHODS

Subjects

CIRRHOTIC PATIENTS WHO were followed up at Kurume University Hospital were enrolled in this study. The inclusion criteria were viral liver cirrhosis, aged less than 70 year and able to undergo neuropsychiatric (NP) tests. The exclusion criteria were a history of overt hepatic encephalopathy and treatment for transjugular intrahepatic portosystemic shunt or esophagogastric varices. Finally, 27 subjects were enrolled in this study.

Informed consent was obtained from all the subjects. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in prior approval by the Ethics Committee of the Kurume University School of Medicine. None of the participants was institutionalized.

NP tests and definition of CD

The subjects underwent NP tests, including the block design test, digit symbol test, and number connection tests A and B. Patients with two or more abnormal results in these tests were defined as having CD, as described previously.[32]

Measurement of biochemical parameters

Venous blood samples were collected in the morning after overnight fasting. Biochemical parameters were measured by conventional clinical methods (Department of Clinical Laboratory, Kurume University Hospital), as described previously.[33,34]

Statistical analysis

Data are expressed as mean ± standard deviation. Nonparametric multiple comparisons were made by the Mann–Whitney *U*-test. Categorical comparisons were made by Fisher's exact test. A logistic regression model was used for multivariate stepwise analysis. A decision-tree algorithm was constructed, and the categorical differences in the decision-tree model were analyzed by χ^2-tests, as described previously.[25,26] The level of statistical significance was set at $P < 0.05$.

RESULTS

Analysis of bioparameters associated with CD

THE CHARACTERISTICS OF patients with and without CD are shown in Table 1. Univariate analysis revealed no significant differences between cirrhotic patients with and without CD in age, sex or Child–Pugh grade. No significant differences were observed between patients with and without CD in biochemical parameters such as the ammonia level, branched-chain amino acid/tyrosine ratio, zinc level or Homeostasis Model of Assessment – Insulin Resistance (HOMA-IR) value. In addition, fasting glucose and HOMA-IR were not significantly different between CD and non-CD patients with fasting glucose of less than 140 mg/dL ($P = 0.9096$ in fasting glucose and $P = 0.7055$ in HOMA-IR).

Multivariate stepwise analysis identified the levels of total bilirubin, triglycerides and free fatty acids (FFA) as independent bioparameters associated with the incidence of CD (Table 2).

Decision-tree algorithm for CD

The decision-tree algorithm showed that all the subjects were classifiable into three groups on the basis of two variables (Fig. 1). FFA was selected as the initial split variable with a cut-off value of 514 mEq/L. Among the nine patients with FFA of 514 mEq/L or more, seven

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Table 1 Characteristics of all subjects

	CD	No CD	*P* value
n	14	13	
Age	59.8 ± 8.0	62.8 ± 6.1	N.S.
Sex (F/M)	5/9	7/6	N.S.
Child–Pugh (A/B/C)	12/2/0	7/5/1	N.S.
Aspartate aminotransferase (U/L)	68.8 ± 27.4	63.4 ± 24.7	N.S.
Alanine aminotransferase (U/L)	73.1 ± 74.8	56.0 ± 29.8	N.S.
Alkaline phosphatase (U/L)	416.0 ± 400.2	366.6 ± 187.6	N.S.
γ-Glutamyltransferase (U/L)	87.2 ± 128.5	56.2 ± 39.6	N.S.
Total bilirubin (mg/dL)	1.11 ± 0.49	1.53 ± 0.83	N.S.
Albumin (g/dL)	3.46 ± 0.41	3.32 ± 0.76	N.S.
Prothrombin time (%)	86.4 ± 10.2	74.5 ± 17.3	N.S.
Ammonia (μg/dL)	59.2 ± 25.2	58.1 ± 31.9	N.S.
Fasting glucose (mg/dL)	136.4 ± 60.1	127.8 ± 56.4	N.S.
Hemoglobin A1c (%)	5.8 ± 1.9	5.6 ± 1.3	N.S.
Fasting immunoreactive insulin (μU/mL)	16.8 ± 14.0	13.9 ± 6.8	N.S.
HOMA-IR	6.20 ± 7.41	4.92 ± 5.07	N.S.
Total cholesterol (mg/dL)	157.2 ± 31.3	152.5 ± 29.7	N.S.
Triglyceride (mg/dL)	96.6 ± 33.9	116.4 ± 47.2	N.S.
Free fatty acids (mEq/L)	567.9 ± 272.9	453.5 ± 229.1	N.S.
Iron (μg/dL)	274.8 ± 560.0	160.4 ± 63.0	N.S.
Ferritin (ng/mL)	194.6 ± 248.3	129.5 ± 115.5	N.S.
Zinc (μg/dL)	63.6 ± 9.7	59.8 ± 22.0	N.S.
Branched-chain amino acids/tyrosine ratio	3.54 ± 1.26	3.54 ± 1.60	N.S.

Data are expressed number of mean ± standard deviation.
CD, cognitive dysfunction; HOMA-IR, Homeostasis Model of Assessment – Insulin Resistance; N.S., not significant.

(77.8%) had CD. Meanwhile, among the 18 patients with FFA of less than 514 mEq/L, seven (38.9%) had CD.

Triglycerides were selected as the second split variable with a cut-off value of 106 mg/dL. Among patients with FFA of less than 514 mEq/L, five patients (62.5%) had

Table 2 Logistic regression analysis for CD

	OR	95% CI	*P*-value
Total bilirubin	0.002	5.708e-7–0.154	<0.05
Triglyceride	0.889	0.748–0.964	<0.05
Fee fatty acids	1.015	1.004–1.037	<0.05
Total cholesterol	1.119	1.024–1.323	N.S.
HOMA-IR	2.053	0.889–7.631	N.S.
Zinc	0.915	0.784–1.010	N.S.
Fasting glucose	1.033	0.989–1.102	N.S.
Ammonia	1.063	0.964–1.186	N.S.

CD, cognitive dysfunction; CI, confidence interval; HOMA-IR, Homeostasis Model of Assessment – Insulin Resistance; N.S., not significant; OR, odds ratio.

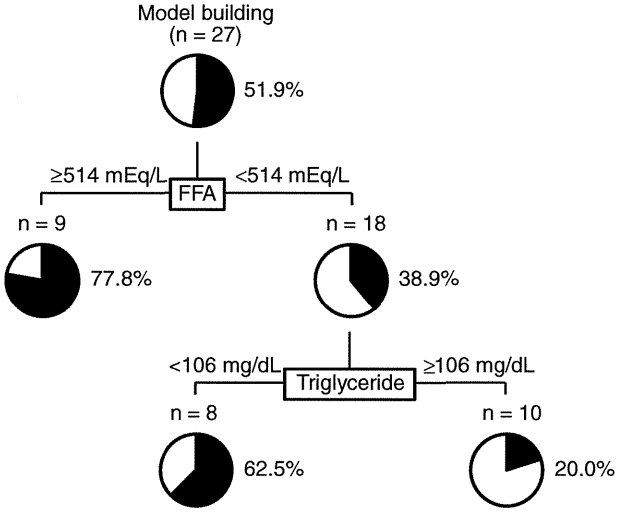

Figure 1 Decision-tree algorithm for cognitive dysfunction (CD). The subjects were classified according to the indicated cut-off values of the variables. The pie graphs indicate the percentage of CD (black)/no CD (white) in each group. FFA; free fatty acids.

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Table 3 Biochemical profiles and the incidence of CD

	CD	No CD
FFA ≥514 mEq/L or triglyceride <106 mg/dL	12	5
FFA <514 mEq/L and triglyceride ≥106 mg/dL	2	8

CD, cognitive dysfunction; FFA, free fatty acids.

CD among the eight patients with triglycerides of less than 106 mg/dL, while two patients (20.0%) had CD among the 10 patients with triglycerides of 106 mg/dL or more.

The distribution of CD differed significantly between the groups ($P = 0.0325$).

Categorical differences according to the decision-tree algorithm for CD

According to the results of the decision-tree algorithm, all subjects were classified into two groups: one group with FFA of 514 mEq/L or more or triglycerides of less than 106 mg/dL ($n = 17$), and another group with FFA of less than 514 mEq/L and triglycerides of 106 mg/dL or more ($n = 10$). The distribution of CD was significantly different between the groups ($P = 0.0183$) (Table 3). The sensitivity, specificity and accuracy using the cut-off values of FFA and triglycerides were 85.7% (12/14), 61.5% (8/13) and 74.1% (20/27), respectively.

DISCUSSION

THE RESULTS OF this study show that FFA and triglycerides were independent risk factors for CD in cirrhotic patients. Furthermore, data-mining analysis revealed that FFA of more than 514 mEq/L or triglycerides of less than 106 mg/dL is a profile associated with the incidence of CD in cirrhotic patients.

Hyperammonemia and inflammation are known to occur in the pathogenesis of CD in cirrhotic patients.[35–38] However, CD is not always correlated with the severity of liver disease, blood levels of ammonia or inflammation,[6] suggesting the presence of other pathogenic factors. In this study, we demonstrated that FFA and triglycerides are associated with the incidence of CD in cirrhotic patients. Although higher serum FFA levels and lower serum triglyceride levels can be thought to reflect hepatic insufficiency, serum albumin levels and blood ammonia were not identified as risk factors for CD in this study. Moreover, FFA and triglycerides were identified as independent risk factors. Although the precise causal relationship between these factors and CD remains unclear, FFA and triglycerides vary with starvation and meal uptake. Malnutrition is associated with CD,[24] and eating breakfast is known to improve CD in cirrhotic patients.[39] Taken together, changes in lipid metabolism caused by starvation or meal uptake may pleiotropically affect the development of CD in cirrhotic patients.

Data-mining analysis provided FFA of more than 514 mEq/L as the initial classification, suggesting that FFA is the most closely related factor to the incidence of CD in cirrhotic patients. Although the relationship between FFA and CD is unclear, there are some possible explanations. Serum albumin is a carrier protein for various substances, including FFA and tryptophan.[40,41] An increase in FFA–albumin binding results in the dissociation of tryptophan from albumin and a subsequent increase in serum-free tryptophan levels.[41–43] Tryptophan can be transported into the brain across the blood–brain barrier and converted to 5-hydroxytryptamine, which is a neurotransmitter known to be associated with hepatic encephalopathy[44,45] as well as cognitive function.[46]

In patients with FFA of less than 514 mEq/L, triglycerides of less than 106 mg/dL was identified as the secondary classification. Contrary to our results, hypertriglyceridemia is a previously established risk factor for CD.[47,48] Although the reason for this discrepancy remains unclear, it can be speculated that hypertriglyceridemia may cause CD via the micro-impairment of cerebrovascular circulation.[49] Meanwhile, triglycerides, particularly medium-chain triglycerides, are structured lipids and good sources of energy in the brain.[50] In fact, patients with hypotriglyceridemia develop complications such as neurological manifestations with structural changes in the nerves.[51,52] Moreover, treatment with medium-chain triglycerides is reported to improve cognitive functioning in older adults with memory disorders.[53] Thus, lower FFA levels may cause CD via structural or functional nerve impairment.

Cognitive dysfunction occurs in up to 80% of patients at any stage of chronic liver disease[24] and is related not only to poor prognosis[54] but also to social issues, including falls and motor vehicle accidents.[10,13,14,16,55,56] Although NP tests are reliable tools for diagnosing CD in cirrhotic patients,[3,57] they are time-consuming (~30 min) and are affected by the educational status. Both electroencephalogram and critical flicker frequency are rapid tests for diagnosing CD. However, these tests require a trained personnel and

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specialized equipment.[6,58] Therefore, a simple screening tool for CD is required for patients with chronic liver disease. In this study, we demonstrated that the lipid profile of FFA of more than 514 mEq/L or triglycerides of less than 106 mg/dL is associated with the incidence of CD with high sensitivity. Because evaluating serum FFA and triglyceride levels are simple objective assessments, further studies will focus on the significance of serum FFA and triglyceride levels as a screening bioparameter set for the presence of CD in patients with chronic liver disease.

The limitation of this study would be related to inclusion criteria. Contrary to expectation, a lower level of total bilirubin was identified as a risk factor. In this study, only the cirrhotic patients with no incidence of overt hepatic encephalopathy were enrolled. Because overt hepatic encephalopathy is generally seen in patients with decompensated cirrhosis or liver failure, the odds ratio of total bilirubin may be influenced by inclusion criteria. CD is also seen in cirrhotic patients with the treatment for overt hepatic encephalopathy; these patients should be included in further study.

In conclusion, the results of this study show that the serum levels of FFA and triglycerides are independently associated with the incidence of CD in cirrhotic patients. In addition, data-mining analysis revealed that FFA of more than 514 mEq/L or triglycerides of less than 106 mg/dL is a profile associated with the incidence of CD in cirrhotic patients. Thus, the lipid profile could be involved in the development of CD and could be considered as a possible screening bioparameter for CD in cirrhotic patients.

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Efficacy, Safety, and Survival Factors for Sorafenib Treatment in Japanese Patients with Advanced Hepatocellular Carcinoma

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Key Words
Sorafenib · Hepatocellular carcinoma · Japanese

Abstract
Background: Sorafenib, an oral multikinase inhibitor, was approved for the treatment of advanced hepatocellular carcinoma (HCC), but has not been adequately evaluated for safety and effectiveness in Japanese patients with advanced HCC. ***Aims:*** The purpose of this study was to prospectively assess the efficacy, safety, and risk factors for survival in patients with advanced HCC treated with sorafenib. ***Methods:*** Between May 2009 and December 2010, 96 Japanese patients with advanced HCC (76 male, 20 female, mean age: 70.4 years) were treated with sorafenib. Eighty-eight patients had Child-Pugh class A, and 8 patients had Child-Pugh class B liver cirrhosis. Barcelona Clinic Liver Cancer stage B and C were found in 64 and 32 patients, respectively. ***Results:*** Twelve patients demonstrated partial response to sorafenib therapy, 43 patients had stable disease, and 33 patients had progressive disease at the first radiologic assessment. The most frequent adverse events leading to discontinuation of sorafenib treatment were liver dysfunction (n = 8), hand-foot skin reaction (n = 7), and diarrhea (n = 4). The median survival time and time to progression were 11.6 and 3.2 months, respectively. By multivariate analysis, des-γ-carboxy prothrombin serum levels and duration of treatment were identified as independent risk factors for survival. ***Conclusions:*** This study showed that sorafenib was safe and useful in Japanese patients with advanced HCC. In addition, this study demonstrated that sorafenib should be administered as a long-term treatment for advanced HCC regardless of therapeutic effect and dosage.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world [1–3]. Recent advances in imaging have enabled an increased detection rate for early-stage HCC. By detecting HCC at an early stage, curative therapies, such as hepatic resection, liver transplantation, and radiofrequency ablation, are possible,

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which improve patient survival rates [4, 5]. In Japan, transarterial chemoembolization is an important locoregional treatment for patients with unresectable HCC [6]. However, long-term survival remains limited due to high rates of recurrence, even after these curative therapies [7, 8]. In particular, the development of advanced HCC with macroscopic vascular invasion or extrahepatic metastasis greatly reduces survival rates as effective systemic therapies have not been developed to date [9–11].

Recently, sorafenib, an oral multikinase inhibitor, has become available as a new molecular targeted therapy for advanced HCC. The magnitude of the benefit obtained with sorafenib (25–35% decreased risk of death) is similar to that observed with trastuzumab in breast cancer, bevacizumab in colon cancer, or erlotinib in lung cancer [12–14]. Sorafenib has been shown to suppress tumor growth and angiogenesis by inhibiting the Raf/MEK/ERK signaling pathway and by inhibiting receptor tyrosine kinases, such as vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, and platelet-derived growth factor receptor-β (PDGFR-β) [15].

The introduction of sorafenib has changed the standard systemic therapy for advanced HCC, as demonstrated by the recent positive results from randomized controlled trials, and this new treatment was approved in Japan in May 2009 [16, 17]. These results, proving the efficacy of molecular targeted therapies for liver cancer, have triggered the search for additional molecular agents to further improve patient survival. However, concerns regarding the development and approval of new molecular targeted therapies, including sorafenib, include the inclusion and exclusion criteria for the trials and frequent adverse events. The SHARP trial was conducted at 121 centers in 21 countries in Europe, North America, South America, and Australasia [16], and 23 centers in China, South Korea, and Taiwan were enrolled in the Asia-Pacific study [18], but no trials have been performed in Japan. Moreover, these studies did not primarily include patients infected with hepatitis C virus (HCV). In Japan, >70% of HCC cases are related to chronic liver disease with HCV infection. Therefore, in this study, we prospectively assessed the efficacy and safety of sorafenib and identified the factors associated with improved survival in Japanese patients with advanced HCC primarily due to HCV infection.

Patients and Methods

Patients

Eligibility criteria for this study were as follows: (1) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; (2) measurable disease using the Response Evaluation Criteria in Solid Tumors (RECIST); (3) Child-Pugh class A or B; (4) leukocyte count ≥2,000/mm^3; (5) platelet count ≥50 × 10^9/l; (6) hemoglobin level ≥8.5 g/dl; (7) serum creatinine level <1.5 mg/dl, and (8) no ascites or encephalopathy. Between May 2009 and December 2010, 96 patients diagnosed with advanced HCC were included in this study. HCC was either confirmed on histology or diagnosed using noninvasive criteria according to the European Association for the Study of Liver. Included patients were treated with sorafenib at 1 of the 12 experienced member institutions of the Kurume Liver Cancer Study Group of Japan: Asakura Medical Association Hospital, Chikugo City Hospital, Kurume Daiichi Social Insurance Hospital, Kurume University Medical Center, Kurume University School of Medicine, Kyushu Medical Center, Ōmuta City Hospital, Saga Social Insurance Hospital, Social Insurance Tagawa Hospital, St. Mary's Hospital, Tobata Kyouritsu Hospital, or Yame General Hospital. The primary outcome of this study was overall survival time. Overall survival time was defined as the time from sorafenib initiation to the date of death or the patient's last follow-up. Relevant data from the patients' clinical records, including history, laboratory results, radiologic findings, histologic results, and survival data, as well as the dosage and adverse events associated with sorafenib therapy, were prospectively collected. The study protocol was approved by University hospital Medical Information Network (UMIN) Center (No. UMIN000007427) and conformed to the guidelines of the 1975 Declaration of Helsinki. Patients were given full information regarding the details of the clinical study, and they provided written informed consent prior to participation in the study.

Diagnosis of Intrahepatic Lesions and Extrahepatic Metastasis

Intrahepatic lesions and vascular invasion were diagnosed using a combination of contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and digital subtraction angiography. In addition, determination of α-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), and des-γ-carboxy prothrombin (DCP) serum levels was performed up to 1 month prior to treatment. Intra-abdominal metastases were detected on abdominal CT, MRI, and ultrasonography, which were performed to evaluate intrahepatic lesions. Pulmonary lesions were detected on chest radiography or chest CT, which were routinely performed up to 1 month prior to treatment. Additional examinations, such as bone scintigraphy and brain CT or MRI, were indicated when symptoms attributable to extrahepatic metastasis appeared. These examinations were also undertaken when AFP, AFP-L3, or DCP were elevated, and the elevation could not be accounted for by the status of the intrahepatic lesions [11]. Tumor stage was classified according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [19].

Sorafenib Treatment

An initial sorafenib dose of 400 mg was orally administered twice daily. Discontinuation and dose reduction were based on tolerance. Side effects of sorafenib were determined via the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [20]. Treatments were discontinued upon development of grade 3 or higher adverse events according to CTCAE classification with the exception of platelet counts and leukocyte counts of <25 × 10^9/l and <1,500/mm^3, respectively.

Table 1. Baseline clinical characteristics

Patient characteristics	n
Age, <70/≥70 years	39/57
Sex, male/female	76/20
Etiology, HBV/HCV/both negative	20/59/17
Child-Pugh class, A/B	88/8
BCLC stage, B/C	64/32
AFP, <1,000/≥1,000 ng/ml	62/34
DCP, <1,000/≥1,000 mAU/ml	49/47

HBV = Hepatitis B virus.

Assessment of Tumor Response

To assess tumor response, 4 weeks after beginning the administration of sorafenib and every 4–6 weeks thereafter, an imaging study was performed. Tumor response was evaluated according to the RECIST criteria, version 1.1 [21] as follows: complete response, all measurable lesions disappeared for >4 weeks; partial response (PR), the sum of the diameters of the largest target lesions decreased by >30% and there was no development of a new lesion for >4 weeks; progressive disease (PD), the sum of the largest diameters increased by >20% or a new lesion appeared, and stable disease, neither PR nor PD was seen [22]. Cancer in patients who died before their first radiographic assessment was classified as PD. The time to radiologic progression was defined as the time from sorafenib initiation to disease progression. Data from patients who died without tumor progression were censored. The disease control rate was defined, on the basis of independent radiologic review, as the percentage of patients whose best-response RECIST rating of complete response, PR, and stable disease was maintained for at least 30 days after the first demonstration of that rating.

Statistical Analysis

Baseline patient characteristics were analyzed using descriptive statistical methods. Survival curves were calculated via the Kaplan-Meier method. Univariate survival curves were compared using the log-rank test. A p value <0.05 was considered statistically significant. All analyses were performed using the statistical software package SPSS (IBM, Armonk, N.Y., USA). The Cox proportional hazards model was used to evaluate the interaction between baseline characteristics and the effect of sorafenib on overall survival.

Results

Patient Characteristics

There were 76 male (79%) and 20 female (21%) patients, with a mean age of 70.4 (range 33–87) years (table 1). Chronic HCV infection was the predominant cause of liver disease (n = 59; 61%), followed by chronic hepatitis B virus infection (n = 20; 21%). Eighty-eight (92%) patients had Child-Pugh class A, and 8 (8%) patients had Child-Pugh class B liver cirrhosis. With respect to tumor stage, 64 (67%) patients had stage B disease and 32 (33%) patients had stage C disease, according to the BCLC staging classification [19]. The most frequent sites of extrahepatic metastases were the lung (n = 41), bone (n = 14), and lymph nodes (n = 12). Prior to sorafenib therapy, 88 (92%) patients had been treated with surgical, loco-regional, or pharmacologic therapies. Of these 88 patients, 48 received transcatheter arterial infusion chemoembolization, 34 received hepatic arterial infusion chemotherapy, 25 underwent hepatic resection, and 23 patients underwent radiofrequency ablation.

Overall Response and Efficacy

The mean duration of oral treatment was 4.2 (range 0.1–16.2) months, and the mean follow-up duration was 6.4 (range 0.1–16.2) months. Forty (42%) patients died during the observation period, whereas 56 (58%) patients were alive at the end of the follow-up period. At the first radiologic assessment, 12 (13%) patients showed PR, 43 (45%) patients showed stable disease, and 33 (34%) patients showed PD; 8 (8%) patients had no follow-up radiologic evaluation and were not included in further analysis.

Treatment Compliance

Performance status was used to determine initial sorafenib dose at the discretion of each chief physician. Fifty-eight patients with a performance status of 0 started treatment with 800 mg sorafenib daily and 38 patients with a performance status of 1 began with a 400-mg daily dose of sorafenib. Dose reduction was necessary in 40 patients during treatment. By December 2010, the end of the follow-up period, 71 patients had discontinued treatment. The reasons for discontinuation were adverse events (36 patients), radiologic and symptomatic progression (27 patients), and deterioration in performance status (8 patients). The mean duration of treatment, prior to discontinuation, was 3.5 (range 0.1–15.5) months.

Treatment-Related Toxicities

Hand-foot skin reaction (HFSR) was the most troublesome adverse event in our series, occurring in 49 (51%) patients. Other frequent toxicities included diarrhea (n = 23; 24%), alopecia (n = 13; 14%), liver dysfunction (n = 13; 14%), and fatigue (n = 11; 11%). The most frequent adverse events leading to discontinuation of sorafenib treatment were HFSR (n = 7; 7%), diarrhea (n = 4; 4%), and liver dysfunction [n = 8; 8%; 7 patients with Child-Pugh class A disease (8%) and 1 with Child-Pugh class B (13%)]. In par-

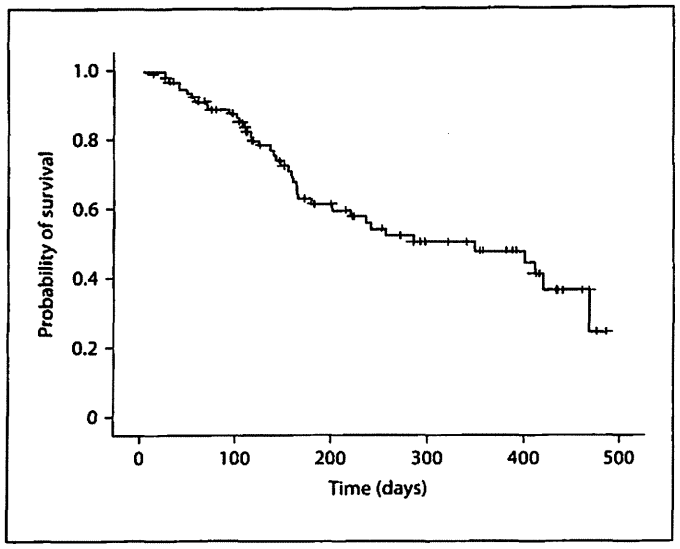

Fig. 1. Cumulative survival of 96 patients with advanced HCC treated with sorafenib. The MST of these patients was 11.6 months. The 1-year survival rate was 48%.

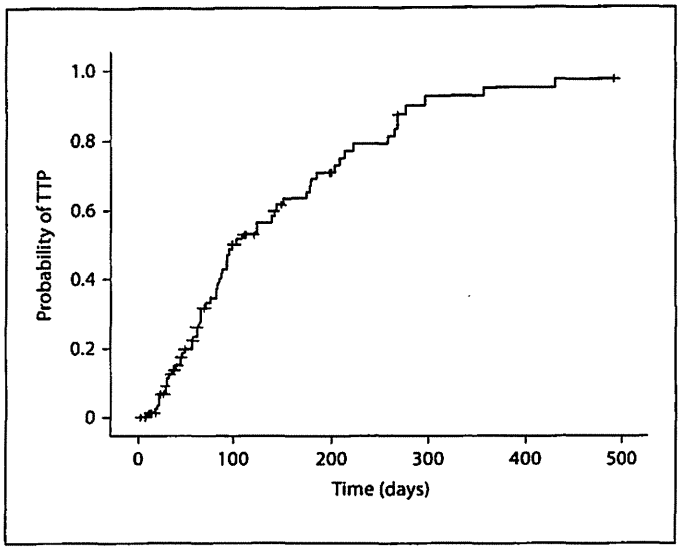

Fig. 2. Cumulative progression of 96 patients with advanced HCC treated with sorafenib. The median TTP of these patients was 3.2 months.

Table 2. Univariate and multivariate analyses of survival in patients with HCC

	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥70 years)	1.091 (0.581–2.050)	0.786		
Sex (male)	0.670 (0.320–1.403)	0.288		
Child-Pugh class (B)	2.273 (0.868–5.952)	0.094		
AFP (≥1,000 ng/ml)	1.953 (1.046–3.647)	0.036		
DCP (≥1,000 mAU/ml)	2.723 (1.394–5.316)	0.003	2.722 (1.369–5.412)	0.004
Daily average dosage (≥400 mg)	0.970 (0.503–1.870)	0.927		
Daily average dosage (≥600 mg)	1.042 (0.556–1.954)	0.898		
Duration of treatment (≥30 days)	0.403 (0.199–0.816)	0.012	0.407 (0.196–0.848)	0.016
Therapeutic effect (PD)	1.876 (0.991–3.549)	0.053		

HR = Hazard ratio; 95% CI = 95% confidence interval.

ticular, interstitial pneumonia (n = 1; 1%) and tumor lysis syndrome (n = 1; 1%) were serious adverse events. The single case of interstitial pneumonia resulted in death.

Survival and Factors Associated with Outcome

The cumulative survival curve of 96 patients is shown in figure 1. The median survival time (MST) was 11.6 (range 0.1–16.2) months, with a 1-year survival rate of 48%. The median time to progression (TTP) was 3.2 (range 0.1–16.2) months (fig. 2). Cox proportional hazards regression analysis was performed to identify independent factors associated with survival (table 2). The results of univariate analysis showed that AFP serum level (≥1,000 ng/ml, p = 0.036), DCP serum level (≥1,000 mAU/ml, p = 0.003), and duration of treatment (>30 days, p = 0.012) were significant risk factors adversely impacting survival. Multivariate analysis showed that DCP serum level (≥1,000 mAU/ml, HR 2.722, 95% CI 1.369–5.412, p = 0.004) and duration of treatment (>30 days, HR 0.407, 95% CI 0.196–0.848, p = 0.016) were independent risk factors for decreased survival. Cumulative survival curves, plotted for DCP serum level and duration of treatment, are shown in figure 3.

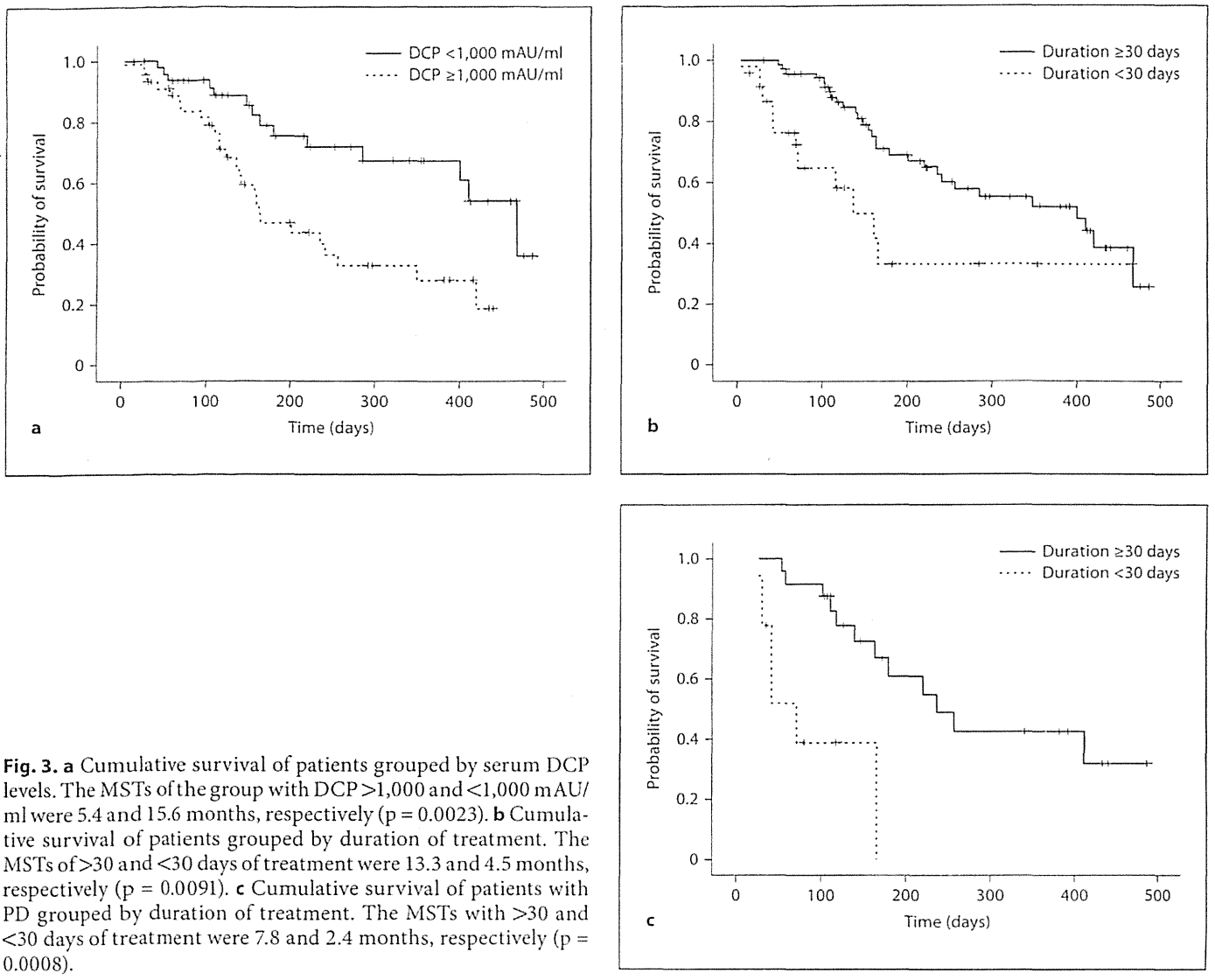

Fig. 3. a Cumulative survival of patients grouped by serum DCP levels. The MSTs of the group with DCP >1,000 and <1,000 mAU/ml were 5.4 and 15.6 months, respectively (p = 0.0023). **b** Cumulative survival of patients grouped by duration of treatment. The MSTs of >30 and <30 days of treatment were 13.3 and 4.5 months, respectively (p = 0.0091). **c** Cumulative survival of patients with PD grouped by duration of treatment. The MSTs with >30 and <30 days of treatment were 7.8 and 2.4 months, respectively (p = 0.0008).

Discussion

Sorafenib, an oral multikinase inhibitor, has recently become available as a new molecular targeted therapy for advanced HCC. A significant survival benefit and good tolerance was demonstrated with sorafenib treatment for patients with advanced HCC in 2 randomized phase III placebo-controlled trials [16, 18]. Consequently, sorafenib has become the standard treatment for advanced HCC in the United States, Europe, and many other countries, including Japan. This study prospectively assessed the efficacy and safety of sorafenib and identified the factors associated with survival in Japanese patients with advanced HCC. In this study, the TTP and MST of Japanese patients receiving sorafenib were 3.2 and 11.6 months, respectively. TTP in this study was shorter than that observed in the SHARP trial (5.5 months) and was similar to that observed in the Asia-Pacific study (2.8 months) [16, 18]. However, the MST in the current study was longer than that observed in the Asia-Pacific study (6.5 months) and was similar to that observed in the SHARP trial (10.7 months) [16, 18]. Compared with these 2 previous studies, the time between TTP and MST was longer in the current study, though the reason for this is unclear.

An exploratory multivariate analysis with the use of a Cox proportional hazards model identified 2 baseline patient characteristics that were prognostic indicators for overall survival: duration of treatment and serum DCP

level. In contrast, therapeutic effect and dosage of sorafenib were not significant risk factors adversely affecting survival in this study. In the SHARP trial and the Asia-Pacific study, administration of sorafenib was continued until the occurrence of both radiologic and symptomatic progression, or the occurrence of either unacceptable adverse events or death [16, 18]. In the current study, neither radiologic nor symptomatic progression were criteria for discontinuation. The difference in the discontinuation criteria may explain the gap between TTP and MST in this study. Even with tumor progression, the patients who continued on sorafenib may have had better survival potential compared to the patients in whom sorafenib was discontinued (fig. 3c). Therefore, this study suggests that sorafenib should be administered long-term in patients with advanced HCC independent of therapeutic effect and dosage.

Previous studies reported that for patients with HCC, high serum DCP levels are associated with vascular invasion, metastasis, and tumor recurrence [23]. Hypoxia has been reported to induce epithelial mesenchymal transition or cytoskeletal changes. Indeed, hypoxic stimulation induced hepatoma cell lines (HepG2 or PLC/PRF/5 cells) to undergo epithelial-to-fibroblastoid conversion or epithelial mesenchymal transition, and these cells produced DCP [23]. Therefore, DCP as an HCC tumor marker is more useful in larger tumors which are likely to be exposed to hypoxia during tumor development [23]. Thus, it is suggested that higher serum DCP levels represent a more advanced state of HCC, and, as a result, lead to reduced survival rates.

In this study, disease classification at the first radiologic assessment was PR for 12 (13%) patients, stable disease for 43 (45%) patients, and PD for 33 (34%) patients. Notably, the proportion of patients with PR in our study was higher compared to the SHARP trial (2%) and the Asia-Pacific study (3.3%). It is not clear why there appears to be a higher rate of PR in Japanese patients. Previous studies suggested that there may be racial differences in terms of gene mutations that may affect sorafenib treatment [24, 25]. Lynch et al. [26] reported that patients with non-small-cell lung cancer have specific mutations in the *EGFR* gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib. Therefore, it is suggested that Japanese patients with advanced HCC may be more sensitive to sorafenib than Western and other Asian populations. To investigate the possible differences in the therapeutic effects of sorafenib, further studies with larger patient populations will be needed.

Treatment-related adverse events were a substantial issue impacting the continuation of treatment with sorafenib. In this study, although the overall incidence of treatment-related adverse events was high (90%), events were primarily controlled with medical treatment and/or sorafenib dose reductions. Adverse events leading to discontinuation of treatment included liver dysfunction (8%), HFSR (7%), and diarrhea (4%), which are commonly associated with sorafenib [27, 28]. However, in the SHARP trial, the overall incidence of treatment-related adverse events was 80% in the sorafenib group, and the most frequent adverse events leading to discontinuation of sorafenib treatment were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%) [16]. HFSR is particularly well known as an early adverse event [29–31] associated with sorafenib therapy and the severity of HFSR depends on the duration of treatment, dosage, and accumulation of the drug [32]. Further effort put towards the effective control of adverse effects and management of sorafenib dosing, with a priority given to facilitating long-term administration, will lead to the most effective therapy for patients with HCC. Moreover, hepatic reserve is important for hepatic extraction and metabolism of sorafenib. In this study, liver dysfunction necessitating suspension or discontinuation of sorafenib occurred with similar frequency in patients with Child-Pugh class B and Child-Pugh class A disease. This result suggests that sorafenib can be used in patients with Child-Pugh class B, as well as in patients with Child-Pugh class A disease.

In conclusion, sorafenib was a safe and effective therapy in Japanese patients with advanced HCC. In addition, duration of treatment and serum level of DCP were independent risk factors negatively impacting survival in this study. The results of this study indicate that sorafenib should be administered as a long-term treatment for advanced HCC in patients regardless of therapeutic effect and dosage.

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