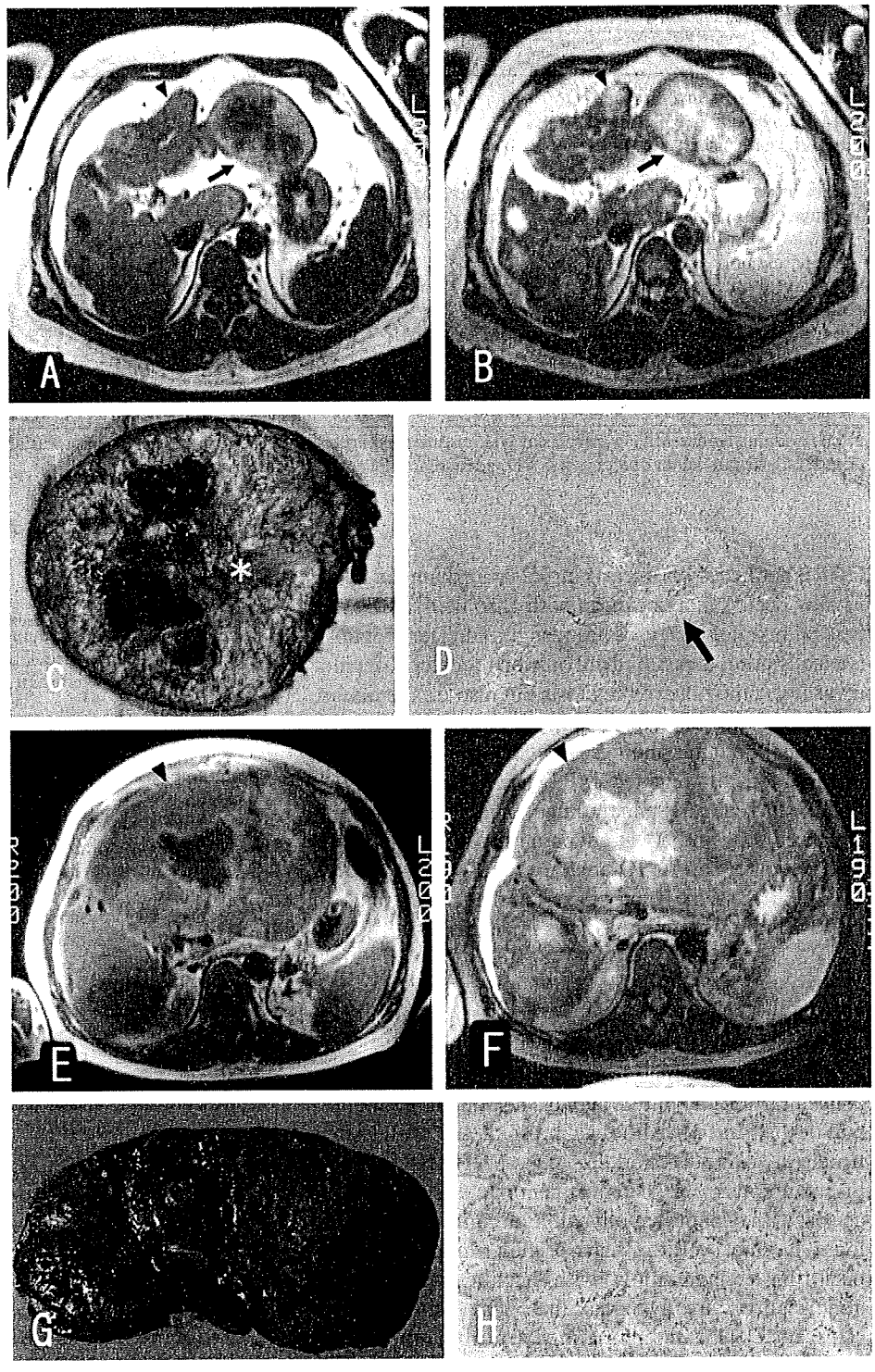
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Table 3. Coexistence of vascular disorders and hepatocellular nodules

Vascular disorder	Hepatic hemodynamic abnormality
Hepatic arterial inflow disorder	
Vasculitis/angiitis (collagen disease)	NRH
Arteriovenous shunt (Rendu-Osler-Weber disease)	NH
Portal vein inflow disorder	
Extrahepatic portal vein occlusion/portal vein thrombosis	FNH, NRH, PNT
Congenital absence of the portal vein (complete/partial)	FNH, NRH, Ad, HCC
Intrahepatic portosystemic shunt	FNH, AD
Idiopathic portal hypertension	NRH
Hepatic vein outflow disorder	
Venoocclusive disease	NRH
Budd-Chiari syndrome/hepatic vein thrombosis	FNH, AD, HCC
Presence of the third inflow	
Parabiliary venous system (aberrant right gastric vein)	HPC
Cholecystic vein	HPC

NRH, nodular regenerative hyperplasia; NH, nodular hyperplasia; FNH, focal nodular hyperplasia; PNT, partial nodular transformation; HCC, hepatocellular carcinoma; AD, adenoma; HPC, hyperplastic change

HCC is defined as one measuring <2 cm in diameter. HCC usually occurs in association with chronic liver disease. Several histological types are recognized. The prognosis is usually poor, depending not only on the extent of tumor invasion at the time of diagnosis but also on the disease state of the noncancerous hepatic parenchyma.

Typical imaging findings of HCC are variable signal intensity on T1-weighted MRI, hyperintensity on T2-weighted MRI, early enhancement on dynamic contrast-enhanced CT and MRI, hypodensity on CTAP, and hyperintensity on SPIO-enhanced T2-weighted MRI. SLD-CTHA studies have suggested that the drainage of HCC is mainly through portal venules (Fig. 18).[78]

Conclusion

Hepatocellular nodular lesions may coexist with various congenital and acquired hepatic hemodynamic abnormalities (Table 3). Although most of the nodules are benign regenerative nodules (e.g., FNH, NRH), neoplastic nodules (e.g., hepatic adenoma, HCC) also may coexist with hepatic hemodynamic abnormalities. Radiologically, most of the hepatocellular nodular lesions occurring concomitantly with hepatic hemodynamic abnormalities are hypervascular mass lesions (except NRH and PNT). Differentiating HCC from other hypervascular regenerative nodular lesions is particularly critical. SPIO-enhanced MRI is particularly useful for differentiating hyperplastic lesions from neoplastic lesions.

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内科的治療
化学療法　肝動注化学療法(TAI)

Low dose FP(5-FU+CDDP)肝動注療法

Hepatic arterial infusion chemotherapy using low dose cisplatin and 5-fluorouracil for patients with advanced hepatocellular carcinoma

安東栄治[1]　田中正俊[2]　佐田通夫[1]

Key words：肝細胞癌，門脈腫瘍栓，肝動注化学療法，low dose FP肝動注療法

はじめに

肝動注化学療法が進行肝細胞癌患者の予後を延長することを実証したエビデンスはなく，また全身化学療法と比べて有用であるという十分な科学的根拠もない．しかしながら，肝動注化学療法は我が国では広く用いられており，効果が得られた症例は予後の改善が期待され長期生存例も報告されている．

本稿では，進行肝細胞癌に対するlow dose FP(5-FU+CDDP)肝動注療法の長期治療成績について述べる．

1. Low dose FP肝動注療法の報告とその適応

進行肝細胞癌患者に対するlow dose FP肝動注療法は主に我が国，韓国，台湾で行われその治療成績が報告されている[1-8]．肝動注化学療法全体的にいえることであるが，low dose FP肝動注療法も無治療群を対象とした無作為比較試験の報告はなく，肝癌診療ガイドライン[9]では推奨度グレードC1(行うことを考慮してもよいが，十分な科学的根拠がない)に分類される．門脈腫瘍栓合併例での第2相試験の報告が多く，その直接治療効果は14-48％であった．無治療例と比較した報告[5]では治療群40例の生存期間中央値は5カ月で無治療群39例の3カ月と比較して有意に予後が良好であったと報告している．これらの報告の生存期間中央値は5-10カ月であり，長期生存の観点からすれば満足できる結果とはいいがたい．このため適応症例の選択が重要となるが，予後因子として直接治療効果および肝予備能が最も重要である[1-3]．しかしながら，治療前にlow dose FP肝動注療法の治療効果を確実に予測できる方法は確立していない．したがって，low dose FP肝動注療法の適応は他の標準的治療法(肝切除術，局所療法，肝動脈塞栓術(TACE))の適応外である症例すなわち脈管侵襲陽性例やびまん型肝細胞癌，もしくはTACEが無効であった肝内多発病変の肝細胞癌である．肝予備能良好で，血小板数7万/mm³以上，白血球数3,000/mm³以上の症例が良い適応と考えられるが，Child-Pugh class Bの肝予備能で，血小板数5万/mm³以上，白血球数2,500/mm³以上で導入可能である．

[1]Eiji Ando, Michio Sata: Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine　久留米大学医学部 内科学講座 消化器内科部門　[2]Masatoshi Tanaka: Hepatology and Gastroenterology, Kurume University Medical Center　久留米大学医療センター 消化器科

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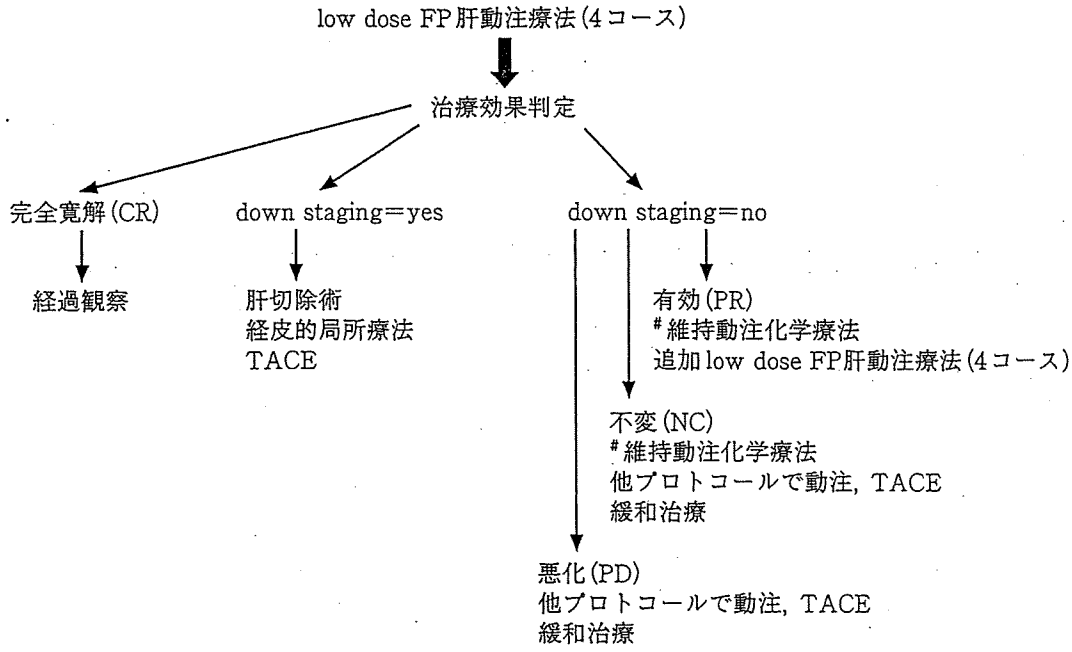

図1 Low dose FP肝動注療法後の治療方針

#維持動注化学療法：CDDP 10-20 mg/day(1 hr)+5-FU 250-500 mg/day(3-5 hr)を2週ごとに繰り返す.

2. Low dose FP肝動注療法の方法と追加治療

low dose FP肝動注療法を行う場合は皮下埋め込み式リザーバーシステムの導入が必須となる. 我が国では多くの施設でこの治療法が可能となっているが, リザーバーシステムの留置および管理の際には様々な合併症を認めることがあるので経験豊富な医師の管理下に行われなければならない. 皮下埋め込み式リザーバーシステムの導入後, low dose FP肝動注療法を開始する. CDDP 10 mg+5-FU 250 mg/body/day, 5日連日, 2日休薬を1コースとして4コース連続を原則とする. 骨髄抑制や副作用出現の場合は休薬期間を設け, 計4週間のプロトコールの完遂を目標としている.

図1に著者らの施設で行っているlow dose FP肝動注療法後の治療方針を示す. down stagingが得られた症例は速やかにより再現性の高い治療へ移行し, down stagingは得られないが, 腫瘍径の縮小もしくは明らかな腫瘍マーカーの低下を認めた症例は再度4コースのlow dose FP肝動注療法(集中動注)を行うかもしくは維持動注化学療法を行っている.

3. 当科でのlow dose FP肝動注療法の治療成績

1990-2001年に当院およびその関連施設でlow dose FP肝動注療法を行った160例の長期治療成績を示す. low dose FP肝動注療法による直接治療効果はCR 15例(9%), PR 55例(34%), NC 59例(37%), PD 31例(19%)で奏効率44%であった. 集中動注でdown stagingが得られた8例(肝切除術2例, 局所療法6例)および集中動注後の維持動注化学療法で10例(計18例(11%))が追加治療により肝細胞癌の消失を認め, 最終的には33例(21%)が一度は肝細胞癌の消失を認めた. 現在156例が死亡し4例が生存中であるが, その長期予後は生存期間の中央値16.4カ月で, 1年生存率64%, 2年生存率36%, 3年生存率25%, 5年生存率10%であった. 多変量解析による予後因子の検討ではChild-Pugh class(p=0.006, リスク比0.597, 95% CI 0.408-0.863), 腫瘍進行度(p=0.046, リスク比1.661, 95% CI 1.008-2.738)および直接治療効果(p<0.0001, リスク比0.360, 95

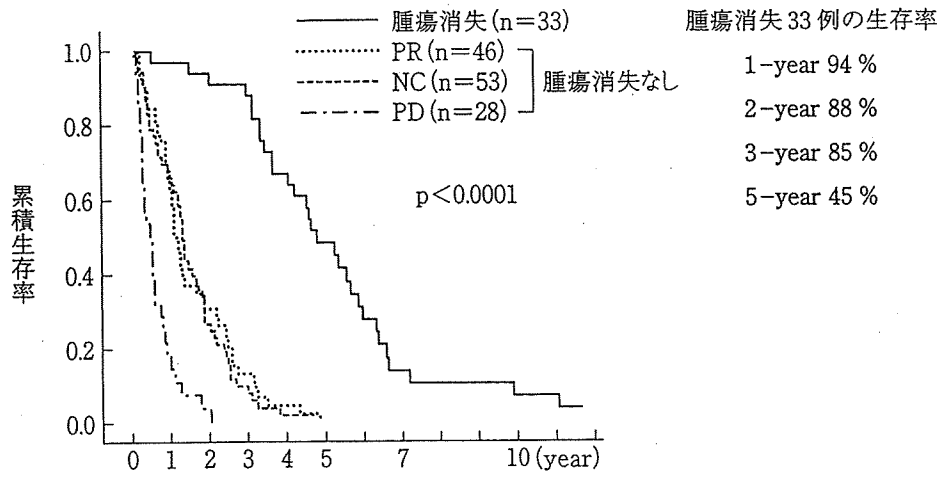

図2 Low dose FP肝動注療法を行った160例の最終治療効果における予後の比較

% CI 0.240-0.541)が独立した予後因子として認識された．興味深かったのは門脈腫瘍栓の有無および腫瘍肉眼型はいずれも単変量解析および多変量解析でも有意な予後因子として認識されず，門脈腫瘍栓合併例の5年生存率9％は門脈腫瘍栓非合併例の5年生存率10％と同等であった．low dose FP肝動注療法は門脈腫瘍栓合併例やびまん型や塊状型肝細胞癌症例に対しても長期生存例が存在することが認識された．

図2に最終治療効果による予後の比較検討を行った．最終的に肝細胞癌が消失した33例の5年生存率は45％で良好な結果であったが，PR症例でも肝細胞癌が消失しなかった症例はNC症例に極めて近い生存率であった．down stagingが得られた症例に対しては肝細胞癌の消失を目的として速やかに，より再現性の高い肝切除術，経皮的局所療法やTACEへ移行することが患者の生命予後の改善に重要であると考えられる(図1)．

4. 当科でのlow dose FP肝動注療法の合併症

low dose FP肝動注療法の対象症例の大多数は脈管侵襲や肝細胞癌の進展に伴う全身状態の悪化および随伴する肝硬変症を合併しているため様々な合併症を伴いやすい[1-8]．特に注意を要する合併症は肝予備能悪化およびカテーテル感染症で，160例中5例(肝予備能悪化2例，カテーテル感染2例，硬化性胆管炎1例)が治療関連死と考えられた．十分なインフォームド・コンセントを前提としてこの治療は行われるべきで，合併症に対する細心の配慮が必要となる．

最後にlow dose FP肝動注療法でdown staging後マイクロ波凝固壊死療法で肝細胞癌が消失し，以後11年無再発生存中の1例を提示する[10]．

［症　例］

64歳，男性．1996年7月，慢性C型肝炎を背景に発生した肝細胞癌の症例で，肝左葉の塊状型肝細胞癌および肝右葉の多発肝細胞癌を認め，左門脈腫瘍栓も合併していた(図3-a～c)．皮下埋め込み式リザーバー留置後low dose FP肝動注療法を計8コース行い，1997年7月には肝右葉多発肝細胞癌および左門脈腫瘍栓の消失を認め肝左葉塊状型肝細胞癌は縮小した(図3-d～f)．1997年9月，肝左葉残存肝細胞癌に対して開腹下マイクロ波凝固壊死療法を行い肝細胞癌の消失を認め(図3-g)，現在11年間無再発生存中である．

おわりに

肝動注化学療法は無作為比較試験の報告がないためその地位はいまだ確立していない．最近，アメリカ肝臓病学会(AASLD)から質の高い比較試験の基準が報告されている[11]．高度進行肝細胞癌では分子標的治療薬であるソラフェニブ

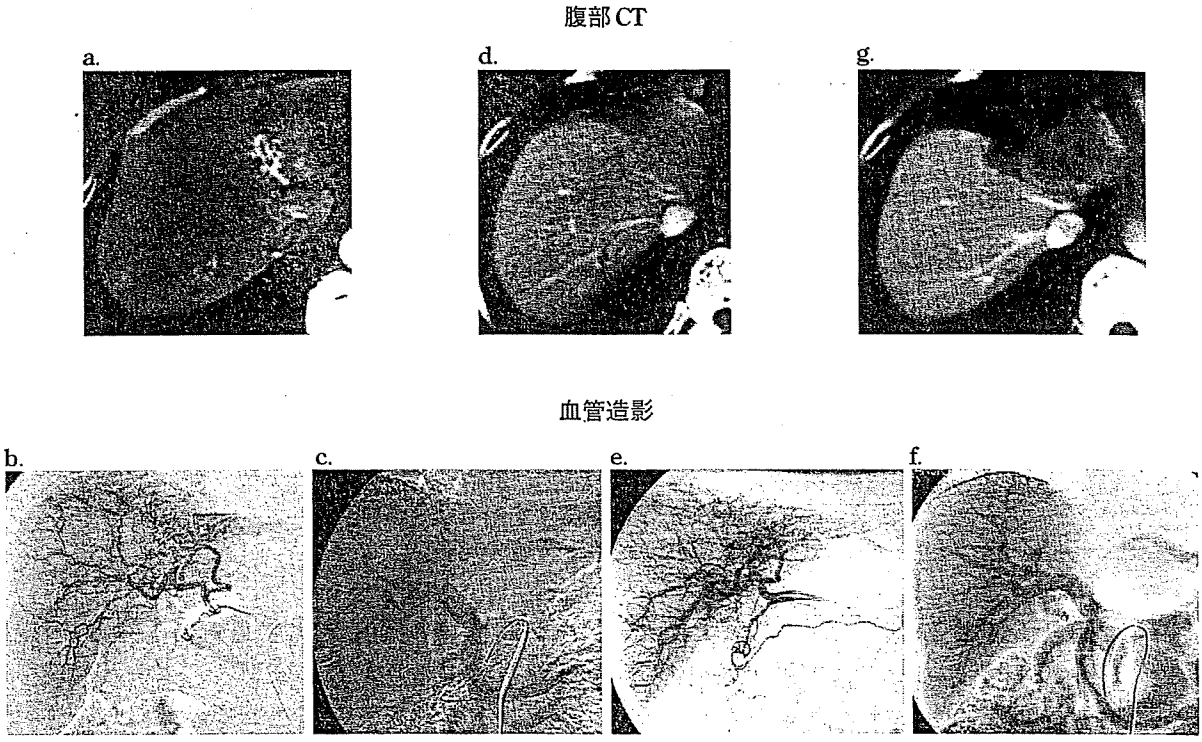

図3 Low dose FP肝動注療法を中心とした集学的治療後11年間無再発生存例

を対象症例として新たな治療法の評価が推奨されている．従来の無治療群を対象症例とする方法と比べてソラフェニブを対象症例とする無作為比較試験は倫理的問題が少なく我が国でも実現可能な方法であると考えられる．肝動注化学療法の有用性を評価するうえで十分な環境が整いつつあり，今後質の高い無作為比較試験が望まれる．

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Original Contribution

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Thrombocytopenia, an Important Interfering Factor of Antiviral Therapy and Hepatocellular Carcinoma Treatment for Chronic Liver Diseases

TAKUMI KAWAGUCHI*,**, RYOKO KURUMATSU**, TATSUYA IDE*,**, EITARO TANIGUCHI**, MINORU ITOU**, MASAHIRO SAKATA**, MITSUHIKO ABE**, SHUJI SUMIE** AND MICHIO SATA*,**

Departments of Digestive Disease Information & Research and Medicine**, Kurume University School of Medicine, Kurume 830-0011, Japan*

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Summary: In patients with chronic liver diseases, thrombocytopenia is a common manifestation which interferes with antiviral therapy for hepatitis C virus (HCV), and with hepatocellular carcinoma (HCC) treatment. While thrombopoietin-receptor agonist is expected to improve thrombocytopenia for patients with chronic liver diseases in 2-3 weeks, there is still a lack of fundamental data about short-term variations in the natural course of platelet count in cirrhotic patients, and the impact of thrombocytopenia on antiviral therapy for HCV-infected patients and patients being treated for HCC. The aims of this study are to investigate sequential changes in platelet count and the impact of thrombocytopenia on antiviral therapy and HCC treatment in patients with chronic liver diseases. A total of 726 chronic liver disease patients were enrolled in this study. Changes of platelet count were examined during a 4-week follow-up. Risk of discontinuation or reduction of peginterferon dosage was evaluated in HCV patients with moderate thrombocytopenia (5-10×$10^4/\mu$L). Risk of platelet transfusion or splenectomy was evaluated in HCC patients with severe thrombocytopenia (<5×$10^4/\mu$L). No significant changes of platelet count were observed in cirrhotic patients with thrombocytopenia during a 4-week follow-up. The rate of discontinuation or reduction in dosage of peginterferon was 85.2% (23/27) in patients with moderate thrombocytopenia. Risk of discontinuation or reduction of peginterferon dosage was 3.4-times higher in HCV patients with thrombocytopenia than in those without thrombocytopenia. In HCC patients with severe thrombocytopenia, the frequency of platelet transfusion or splenectomy during HCC treatment was 57.9% (22/38). Risk of platelet transfusion or splenectomy in HCC patients with thrombocytopenia was 57.9-times higher than in those without thrombocytopenia. In conclusion, we demonstrated no significant variation in the short-term natural course of platelet count in cirrhotic patients. In chronic liver disease patients with moderate and severe thrombocytopenia, about 85% of patients treated with peginterferon, and 60% of patients receiving HCC treatments suffered from thrombocytopenia-related limitations, respectively.

Key words eltrombopag, thrombocytopenia, peginterferon, hepatocellular carcinoma, liver cirrhosis

INTRODUCTION

Thrombocytopenia is a common manifestation in patients with chronic liver diseases [1,2]. Thrombocytopenia is also an exclusion criterion for antiviral therapy in patients with chronic hepatitis C virus (HCV) infection [3]. Development of thrombocytopenia during antiviral therapy also causes discontinuation or reduction of dosage [3,4]. In addition, severe thrombocytopenia interferes with hepatocellular

Corresponding author: Takumi Kawaguchi, MD., PhD., Department of Digestive Disease Information & Research, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Tel: +81-942-31-7902 Fax: +81-942-31-7820 E-mail: takumi@med.kurume-u.ac.jp

Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response.

carcinoma (HCC) treatment [5]. Severe thrombocytopenia has generally been considered a contraindication for hepatectomy [6]. Thus, thrombocytopenia is an important factor that can interfere with clinical treatments in patients with chronic liver diseases. Splenectomy or partial splenic embolization is generally considered an effective therapeutic approach for thrombocytopenia [7-10]. However, these therapeutic procedures are invasive and are not always an option for patients with advanced chronic liver diseases like liver cirrhosis.

There are various theories about thrombocytopenia in chronic liver diseases. Portal hypertension, hypersplenism and bone marrow suppression are factors associated with thrombocytopenia [11,12]. In patients with HCV infection, direct megakaryocyte suppression and antibody-mediated platelet destruction are also involved in the development of thrombocytopenia [12]. In addition, decreased production of thrombopoietin, a hematopoietic growth factor, was recently found to be a causative factor associated with thrombocytopenia in patients with chronic liver diseases [13,14]. Moreover, both interferon and chemotherapy induce decreased platelet count through down-regulation of thrombopoietin production [15,16] and capture of platelets by liver [17,18].

Several new drugs for thrombocytopenia are now under development [19]. A new orally administered thrombopoietin-receptor agonist named eltrombopag increases platelet production through induction of proliferation and differentiation of megakaryocytes *in vivo* [20]. In a phase 1 clinical study of eltrombopag, platelet number began rising at day 5 and peaked at day 15 in healthy male subjects [21]. Results from a randomized placebo-controlled clinical trial showed eltrombopag increased platelet counts in a dose-dependent manner in patients with chronic immune thrombocytopenic purpura [22]. The effectiveness and safety of eltrombopag on thrombocytopenia were demonstrated in a phase II clinical trial in 74 patients with liver cirrhosis [23]. After 4 weeks of treatment platelet counts significantly increased in a dose-dependent fashion. Thus, eltrombopag is the first thrombopoietic drug to safely and consistently increase platelet count in patients with liver cirrhosis. However, there are several issues which need to be considered and clarified before eltrombopag can be generally prescribed and administered to patients with chronic liver diseases. Among these is the question of short-term sequential changes in platelet count in cirrhotic patients. There is currently no available data on weekly changes in platelet count, and therefore it is important to clarify the natural course of platelet count in cirrhotic patients. Another issue is the incidence of thrombocytopenia-related limitations during antiviral therapy and HCC treatment. This type of data will provide basic information for development of new drugs against thrombocytopenia.

The aims of the present study were to investigate 1) short-term sequential changes of platelet count in cirrhotic patients and 2) the impact of thrombocytopenia on antiviral therapy and HCC treatment in patients with chronic liver diseases.

MATERIALS AND METHODS

Subjects

A total number of 726 patients with chronic liver diseases were enrolled in the study. For investigation of short-term sequential changes of platelet count, a case-series study was conducted. Twenty-four (24) patients with liver cirrhosis (age 67.4±10.7; male/female=12/12; HCV-related, n=17; hepatitis B virus-related, n=2; alcoholic, n=1; cryptogenic, n=4) were enrolled via consecutive entry. All patients were hospitalized for treatment of ascites, hepatic encephalopathy, or diabetes mellitus. In order to eliminate treatment effects on platelet count, patients who were treated with interferon, radiofrequency ablation, transarterial chemoembolization, chemotherapy, endoscopic variceal ligation, or endoscopic injection sclerotherapy were excluded. Patients with bacterial infection were also excluded, because inflammation affects platelet count [24].

For investigation of risks of thrombocytopenia-related limitations during antiviral treatment, 190 patients with chronic HCV infection were enrolled. Inclusion criteria were i) antiviral treatment aiming at elimination of HCV, ii) HCV genotype 1b, and iii) HCV viral load >2.0 log IU/mL or >100 KIU/mL. Patients who were receiving low-dose peginterferon for prevention of HCC development were excluded.

For investigation of risks of thrombocytopenia-related limitations during HCC treatment, 512 patients with HCC treated by radiofrequency ablation, transcatheter arterial chemoembolization or hepatic arterial infusion chemotherapy (Child-Pugh grade A, n=371; grade B, n=120; grade C, n=21) were enrolled. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, 1984, and the Declaration of Tokyo, 1975 as reflected in a prior approval by the institutional review committee.

Laboratory determinations

Venous blood samples were taken in the morning after a 12-hour overnight fast. Platelet count, hemoglobin levels, white blood cell count, prothrombin time, and serum levels of alanine aminotransferase (ALT), albumin, total bilirubin, and C-reactive protein (CRP) were measured using standard clinical methods (Department of Clinical Laboratory, Kurume University Hospital) as previously described [25].

Short-term sequential changes of platelet count

During a 4-week follow-up period in patients with liver cirrhosis, sequential changes of platelet count were examined in moderate (5 to $10\times10^4/\mu L$ of platelet count) and severe thrombocytopenia groups ($<5\times10^4/\mu L$ of platelet count) as previously described [26,27]. Platelet count and biochemical parameters were examined once a week for 4 weeks.

Incidence and risk of thrombocytopenia-related limitations during antiviral treatment for HCV

Risk of discontinuation or reduction of peginterferon dosage (peginterferon alfa-2a or peginterferon alfa-2b combined administration with ribavirin) was evaluated retrospectively in HCV patients with moderate thrombocytopenia over their entire treatment period. None of the patients discontinued or reduced peginterferon dosage because of socioeconomic conditions.

Incidence and risk of thrombocytopenia-related limitations during HCC treatment

Inclusion criteria for platelet transfusion and splenectomy were a decrease in platelet count ($<3\times10^4/\mu L$) or an aggravation of hemorrhagic status, such as subcutaneous hemorrhage and gingival hemorrhage. Risk of platelet transfusion or splenectomy during HCC treatment was evaluated retrospectively in patients with severe thrombocytopenia. Patients treated with splenectomy for interferon therapy after HCC treatment were also included.

Statistical analysis

All data are expressed as mean±SD for continuous variables. Statistical significance of changes in parameters during a 4-week period was analyzed by using the Friedman test. Statistical significance of risks of thrombocytopenia-related limitations during interferon and HCC treatments was analyzed by chi-squared test. P values <0.05 were considered significant.

RESULTS

Sequential changes in platelet count

During a 4-week natural course follow-up, there was no significant change in platelet count in any of the patients (Table 1). Serum levels of ALT, albumin, total bilirubin, CRP, and prothrombin time also showed no significant changes in any patients (Table 1). In a stratified analysis, no significant change of platelet count was observed in either the moderate thrombocytopenia group or the severe thrombocytopenia group during a 4-week natural course follow-up (Fig. 1). Levels of other biochemical parameters were not significantly different during a 4-week follow-up in either the moderate thrombocytopenia group or the severe thrombocytopenia group (data not shown).

Incidence and risk of thrombocytopenia-related limitations during interferon treatment

Moderate thrombocytopenia was observed in 14.2%

TABLE 1.
Natural course of biochemical parameters in 24 patients with liver cirrhosis

	Normal range	Week (s) after admission					P
		0	1	2	3	4	
Platelet count ($\times10^4/\mu L$)	13.0 – 36.0	6.2±2.3	5.7±2.0	6.0±2.3	6.1±2.4	6.1±2.3	0.1536
Alanine aminotransferase (U/L)	31 – 33	42±29	37±26	35±19	55±49	37±27	0.5176
Albumin (g/dL)	4.0 – 5.0	2.9±0.7	2.9±0.6	3.0±0.6	3.0±0.4	3.1±0.4	0.5759
Total bilirubin (mg/dL)	0.30 – 1.20	2.0±1.2	1.8±1.2	1.8±1.2	1.7±1.0	1.6±1.0	0.0802
Prothrombin time (%)	60 – 130	70±18	65±17	68±18	69±16	73±20	0.7387
C-reactive protein (mg/dL)	<0.04	0.8±1.3	1.0±1.5	1.1±1.7	0.9±1.4	1.4±2.6	0.8857

Note. Data are expressed as mean ± SD. Statistical significance was analyzed by the Friedman test.

(27/190) of HCV patients receiving combined peginterferon and ribavirin treatment in this study (Table 2). The incidence of discontinuation or reduction in dosage of peginterferon was 85.2% (23/27) due to progression to severe thrombocytopenia ($<5\times10^4/\mu L$). This rate was significantly higher than the incidence of 62.6% (102/163) observed in patients with minor thrombocytopenia or normal range (Table 2). The odds ratio was 3.4. Although the sustained virologic response (SVR) rate was 29.6% in patients with moderate thrombocytopenia, there was no significant difference in SVR rate between patients with and without moderate thrombocytopenia (Table 3).

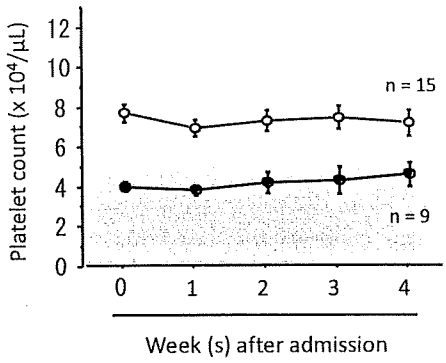

Fig. 1. Sequential measurements of platelet count in cirrotic patients with thrombocytopenia. Moderate thrombocytopenia is indicated as "○" and severe thrombocytopenia is indicated as "●". Values are expressed as mean ± SD. Statistical significance of changes in parameters during a 4-week period was analyzed by using the Friedman test.

Incidence and risk of thrombocytopenia-related limitations during HCC treatment

Severe thrombocytopenia was observed in 3.2% (12/371), 19.2% (23/120), 14.3% (3/21) of HCC patients in Child-Pugh grade A, B, and C groups, respectively. The incidence of platelet transfusion or splenectomy during HCC treatment was 57.9% (22/38) in patients with severe thrombocytopenia. This was significantly higher than the incidence of 2.4% (11/463) seen in HCC patients without severe thrombocytopenia (Table 4). The odds ratio was 57.9.

TABLE 2.
Effects of mild thrombocytopenia before treatment on discontinuation or reduction of peginterferon in patients with chronic hepatitis C

	Discontinuation or reduction		Number of Patients	Odds Ratio	P
	Yes	No			
Platelet count $<10\times10^4/\mu L$	23	4	27	3.439	0.027
Platelet count $\geq10\times10^4/\mu L$	102	61	163		
Number of patients	125	65	190		

Note. Data are expressed as percentage of the total number of patients and number of patients of each category. Statistical significance was analyzed by chi-squared test.

TABLE 3.
Effects of mild thrombocytopenia on sustained viral response rate in patients with chronic hepatitis C

	Sustained virologic response		Number of Patients	Odds Ratio	P
	Yes	No			
Platelet count $<10\times10^4/\mu L$	8	19	27	0.494	0.143
Platelet count $\geq10\times10^4/\mu L$	75	88	163		
Number of patients	83	107	190		

Note. Data are expressed as percentage of the total number of patients and number of patients of each category. Statistical significance was analyzed by chi-squared test.

TABLE 4.
Effects of severe thrombocytopenia on platelet transfusion or splenectomy in cirrhotic patients with hepatocellular carcinoma

	Platelet transfution or splenectomy		Number of Patients	Odds Ratio	P
	Yes	No			
Platelet count $<5\times10^4/\mu L$	22	16	38	57.875	<0.001
Platelet count $\geq5\times10^4/\mu L$	11	463	474		
Number of patients	33	479	512		

Note. Patients treated with splenectomy for initiation of interferon therapy is included. Data are expressed as percentage of the total number of patients and number of patients of each category. Statistical significance was analyzed by chi-squared test.

DISCUSSION

This study demonstrated that there were no changes in platelet count during a 4-week natural course follow-up in patients with chronic liver diseases. About 85% of patients receiving thrombocytopenia-related antiviral treatments either had to discontinue or reduce peginterferon dosage due to clinical thrombocytopenia conditions, and 60% of patients receiving HCC treatment were similarly affected by thrombocytopenia-related limitations.

Although platelet count is unstable and is known to decrease with disease progression in cirrhotic patients [28], no data is available for short-term sequential changes in platelet count in cirrhotic patients. After treatment with eltrombopag, a thrombopoietin-receptor agonist, platelet number begins rising at day 5 and peaks at day 15 [21]. Thus, it is important to clarify the natural course of platelet count in cirrhotic patients before eltrombopag can be generally administrated to patients with chronic liver diseases. In this study, we first demonstrated that platelet count had no significant variation during a 4-week follow-up in patients with liver cirrhosis. Because invasive treatments may affect platelet count, as observed in a previous study [29], hospitalized cirrhotic patients receiving non-invasive treatments were selected for investigation of short-term sequential changes of platelet count. As hepatic inflammation and liver function are also known to affect platelet count [28], laboratory biochemical and liver function parameters were also examined and no significant changes in ALT, albumin, total bilirubin, CRP levels, and prothrombin time were found during a 4-week period. Excluding these factors, the absence of a significant change in platelet count among cirrhotic patients in this study likely reflects the natural course of this disease. Considering that one possible reason for thrombocytopenia is decreased thrombopoietin production in patients with chronic liver diseases [14], administration of eltrombopag, a thrombopoietin-receptor agonist, is expected to be helpful in treating patients with chronic liver diseases at various stages.

Thrombocytopenia can prevent antiviral treatment in patients with chronic HCV infection, however little information is available regarding this issue. In our study, the risk of discontinuation or reduction of peginterferon dosage was about 85% in patients with moderate thrombocytopenia. This was significantly higher than that in patients without moderate thrombocytopenia. Similarly, dose modifications of peginterferon are required in about 20% of patients with no thrombocytopenia [30]. Interferon decreases platelet count through suppression of differentiation in megakaryocytes [16] and capture of platelets by liver [17,18]. A novel thrombopoietin mimetic improves interferon alpha-induced thrombocytopenia *in vivo* [16]. In humans, eltrombopag increases platelet count in cirrhotic patients with HCV infection. Thus, eltrombopag may reduce the risk of discontinuation or reduction of peginterferon dosage in HCV patients.

Although no significant association between moderate thrombocytopenia and SVR rate, which is the rate of continued undetectable serum HCV-RNA 6 months after the completion of anti-viral treatment, was found in our study, Backus et al reported that decreased platelet count is an independent negative predictor for SVR rate in HCV patients treated with peginterferon and ribavirin [31]. The reason for this discrepancy is unclear. However, one possibility is the effect of confounding factors for continuation of

peginterferon. In our study, other factors associated with SVR rate such as sex, age, hepatic fibrosis, and insulin resistance were not matched between patients with and without moderate thrombocytopenia. Thus, these factors may account for the discrepancy between our data and the previous report. Another possibility is differences in administration strategy for peginterferon and ribavirin. In the other study the treatment period was 48 weeks and overall SVR rate was 20.5%. On the other hand, our treatment period was up to 72 weeks and SVR rate was 29.6% even in patients with moderate thrombocytopenia. Thus, prolonged treatment period might have improved the SVR rate, thus eliminating the association between moderate thrombocytopenia and SVR rate.

HCC is now treated with invasive therapies such as resection and radiofrequency ablation, and non-invasive therapies such as chemotherapy [32]. In either case, severe thrombocytopenia seems to adversely affect patient tolerance of these HCC treatments. However, the real incidence of thrombocytopenia-related limitation for HCC treatments is unclear. In our study, about 60% of HCC patients with severe thrombocytopenia received platelet transfusion or splenectomy to improve their thrombocytopenia status. This proportion may be higher than that in other general institutions, because our hospital is a government designated oncology center specializing in HCC. Therefore, we have a relatively high proportion of severe end stage patients desiring intensive care. Although splenectomy and arterial splenic embolization are efficient methods for treating HCC patients with severe thrombocytopenia [7-10], these treatment options are not always available for patients with advanced liver cirrhosis. Thus, severe thrombocytopenia is still a major unresolved issue affecting HCC treatment, and eltrombopag, a thrombopoietin-receptor agonist, is expected to improve HCC treatment.

In conclusion, we demonstrated no change in platelet count during a 4-week natural course follow-up in patients with liver cirrhosis. In patients with moderate and severe thrombocytopenia, about 85% of patients treated with peginterferon and 60% of patients receiving HCC treatment suffered from thrombocytopenia-related limitations, respectively. Since little information is available about short-term sequential changes in platelet count and thrombocytopenia-related limitations on interferon and HCC treatment, this report will provide fundamental information useful when considering administration of eltrombopag to patients with chronic liver diseases.

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BRIEF ARTICLES

Features of hepatocellular carcinoma in cases with autoimmune hepatitis and primary biliary cirrhosis

Takuya Watanabe, Kenji Soga, Haruka Hirono, Katsuhiko Hasegawa, Koichi Shibasaki, Hirokazu Kawai, Yutaka Aoyagi

Takuya Watanabe, Kenji Soga, Haruka Hirono, Katsuhiko Hasegawa, Koichi Shibasaki, Department of Internal Medicine and Gastroenterology, Medical Hospital, The Nippon Dental University School of Life Dentistry at Niigata, 1-8 Hamauracho, Chu-o-ku, Niigata 951-8580, Japan
Hirokazu Kawai, Yutaka Aoyagi, Department of Gastroenterology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi, Chu-o-ku, Niigata 951-8510, Japan
Author contributions: Watanabe T, Soga K, Hirono H, Hasegawa K, Shibasaki K, Kawai H, Aoyagi Y designed the research; Watanabe T, performed the research and analyzed the data; Watanabe T wrote the paper.
Supported by A grant-in-aid from the Ministry of Education, Science, Sports and Culture of Japan
Correspondence to: Takuya Watanabe, MD, PhD, Department of Internal Medicine and Gastroenterology, Medical Hospital, The Nippon Dental University School of Life Dentistry at Niigata, 1-8 Hamauracho, Chu-o-ku, Niigata 951-8580, Japan. nabetaku@dia-net.ne.jp
Telephone: +81-25-2671500 Fax: +81-25-2671582
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Abstract

AIM: To characterize the clinical features of hepatocellular carcinoma (HCC) associated with autoimmune liver disease, we critically evaluated the literature on HCC associated with autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC).

METHODS: A systematic review of the literature was conducted using the Japana Centra Revuo Medicina database which produced 38 cases of HCC with AIH (AIH-series) and 50 cases of HCC with PBC (PBC-series). We compared the clinical features of these two sets of patients with the general Japanese HCC population.

RESULTS: On average, HCC was more common in men than in women with AIH or PBC. While many patients underwent chemolipiodolization (CL) or transcatheter arterial embolization (TAE) (AIH-series: $P = 0.048$ (*vs* operation), $P = 0.018$ (*vs* RFA, PEIT); PBC-series: $P = 0.027$ (*vs* RFA, PEIT), others refused therapeutic interventions [AIH-series: $P = 0.038$ (*vs* RFA, PEIT); PBC-series: $P = 0.003$ (*vs* RFA, PEIT)]. Liver failure was the primary cause of death among patients in this study, followed by tumor rupture. The survival interval between diagnosis and death was fairly short, averaging 14 ± 12 mo in AIH patients and 8.4 ± 14 mo in PBC patients.

CONCLUSION: We demonstrated common clinical features among Japanese cases of HCC arising from AIH and PBC.

Key words: Autoimmune hepatitis; Autoimmune liver disease; Hepatocellular carcinoma; Literature review; Primary biliary cirrhosis

Peer reviewers: Michael Torbenson, MD, Associate Professor of Pathology, Room B314 1503 E Jefferson (Bond Street Building), The Johns Hopkins University School of Medicine, Baltimore, MD 21231, United States; Henning Schulze-Bergkamen, MD, Henning Schulze-Bergkamen, First Medical Department, University of Mainz, Langenbeckstr, 1, 55101 Mainz, Germany

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INTRODUCTION

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerotic cholangitis (PSC) form the triad of autoimmune liver diseases. As defined by Mackay *et al*[1], AIH is a chronic active hepatitis resulting from several distinct autoimmune phenomena. While the anti-inflammatory effects of steroid therapy for this disease may inhibit the promotion of liver carcinogenesis, hepatocellular carcinoma (HCC) does occur rarely in patients with this condition (in about 0.5% of AIH cases)[2,3].

In contrast to AIH, PBC results from an autoimmune mechanism causing chronic cholestasis and chronic non-suppurative destructive cholangitis in medium sized intrahepatic bile ducts[4]. Rare cases of HCC arising from PBC have been reported to date. However,

this association is rare (affecting between 0.3% and 4.22% of cases)[5-11], because a PBC patient's ability to produce regenerative nodules is weak[5-9,12]. Additionally, PBC is pathologically characterized in chronic non-suppurative destructive cholangitis (CNSDC), and the main inflammatory lesions associated with PBC are not hepatocytes, but cholangiocytes, which may be one of the reasons why the incidence of HCC with PBC is low, especially at the early stage when cirrhotic and fibrotic changes do not progress. Recently, reports have suggested that the prevalence of HCC arising from both AIH and PBC is higher than previously believed. In 2001, Caballeria *et al*[13] found that the incidence of HCC in patients with advanced PBC (Scheuer histological stage Ⅲ or Ⅳ) was 11.1%, approximating the 15% incidence in patients with HCV-related cirrhosis (RR 0.812, 95% CI 0.229-2.883). The clinical features of HCC associated with AIH and PBC, however, have not yet been extensively described. Here, we performed a systematic literature review of HCC cases associated with AIH and PBC in Japan, a country with a high burden of autoimmune liver disease. We conducted a critical analysis of case reports to find common themes in the demographic and clinical histories of patients with HCC associated with AIH and PBC.

MATERIALS AND METHODS

We performed a systematic literature review of case reports published in Japan and listed in the Japana Centra Revuo Medicina database, version 3 (systematic literature search system through a computer web site for Japanese literature), using the keywords "hepatocellular carcinoma", "autoimmune hepatitis", and "primary biliary cirrhosis". The database search was limited to the period between 1990 (when the hepatitis C virus was first detected) to the present. The quality of this database available for analysis is thoroughly well-documented. In total, 38 cases of HCC associated with AIH, and 50 cases of HCC associated with PBC were identified. No cases were duplicated, and patients were identified across multiple Japanese medical centers. Most patients in the series had been diagnosed with autoimmune liver disease before HCC was identified. Several cases also presented with co-factors of liver damage and HCC development other than AIH or PBC, such as excessive alcohol intake, HBV, or HCV infection. However, no cases had evidence of hemochromatosis or α1-antitrypsin deficiency. The demographics of these two groups were recorded based on gender, age, period of medical observation, and history of blood transfusion or excessive alcohol intake. Clinical data was also recorded to determine noncancerous pathologies of the liver, HBV or HCV infection status, serum α-fetoprotein (AFP) level, maximal tumor size, history of HCC therapy, clinical outcomes, and cause of death. Cases that did not include a description of alcohol intake were assumed not to have histories of excessive alcohol intake.

We confirmed that all 38 identified cases of HCC associated with AIH met generally accepted international criteria for diagnosis of AIH[14]. Scoring was performed prior to AIH therapy initiation; all scores were greater than 10, and thereby classified as either "probable AIH" or "definite AIH".

Because no internationally accepted diagnostic criteria yet exists for PBC, we utilized the Japanese standard criteria for PBC diagnosis, a standard first proposed in 1992 by a clinical study group supported by the Japanese Ministry of Welfare. According to this standard, PBC diagnosis requires that cases meet at least one of the following criteria: (1) pathologic evidence of CNSDC and positive anti-mitochondrial antibody (AMA) or anti-PDH antibody titers, (2) positive AMA or anti-PDH antibody titers and non-CNSDC pathology compatible with PBC, or (3) no liver biopsy, but, positive AMA or anti-PDH antibody titers and a clinical picture and clinical course compatible with PBC. We confirmed that all 50 identified cases of HCC associated with PBC met the above diagnostic criteria. Six of 50 (12.0%) HCC cases with PBC met the third criteria for PBC, and 44 of 50 (88.0%) cases met the first or second criteria for PBC. The third criteria for PBC remain ambiguous, and it is really hoped that internationally accepted criteria will be determined for PBC diagnosis.

If a case met both generally accepted international criteria for diagnosis of AIH, and the Japanese standard criteria for PBC diagnosis, we diagnosed the case as overlap syndrome. We had two cases of overlap syndrome, and excluded these cases from our analysis.

We did not include a control group, but used the general HCC population in Japan for comparison[15].

Statistical analysis

Intention-to-treat analyses were used throughout, and statistical analysis for categorical comparisons of the data was performed using the program ystat2006.xls for Windows/Macintosh (Igaku Tosho Shuppan Corporation, Tokyo, Japan). We used the χ^2 test and Fisher's exact test for categorical comparisons between patients with HCC associated with AIH or PBC and HCC patients without associated autoimmune disease[15]. The following variables were assessed: gender, HBV or HCV co-infection, history of blood transfusions, history of excessive alcohol intake, positivity for serum-AFP and clinical outcomes. Because the baseline male to female ratio of AIH and PBC was 1:7 and 1:9, respectively, we performed the χ^2 test for males and females separately. We also used the χ^2 test with or without the Yates correction for categorical comparisons of pathological findings of noncancerous lesions of the liver, HCC therapy choices, and cause of death. Where significant differences were noted, χ^2 tests or Fisher's exact tests were repeated with all categorical combinations, using Bonferroni corrections for multiple comparisons. Two tailed Mann-Whitney *U*-tests and *F*-tests were performed at the 5% significance level only for comparisons between HCC patients with AIH and PBC, as the following variables were unavailable for the general HCC

Table 1 Developement period of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/ PBC-series
Observation period (mean ± SD)	Total: 38 1 yr 1 mo-23 yr (10 yr 6 mo ± 6 yr 7 mo)	Total: 49 3 mo-24 yr (9 yr 4 mo ± 6 yr 4 mo)	NA	NA	NA	$P = 0.307$ ($P = 0.815$)
Interval between liver damage and HCC diagnosis (mean ± SD)	Total: 34 0-22 yr 9 mo (10 yr 2 mo ± 6y 5 mo)	Total: 40 0-24 yr (9 yr 9 mo ± 7 yr 0 mo)	NA	NA	NA	$P = 0.740$ ($P = 0.688$)
Period from HCC development to death (mean ± SD)	Total: 18 2 mo-3 yr (1 yr 2 mo ± 12 mo)	Total: 16 0-5 yr (8.4 ± 14 mo)	NA	NA	NA	$P = 0.047$[a] ($P = 0.401$)

The *P*-value above was calculated from the Mann-Whitney *U*-test and the *P*-value below, indicated in parentheses, was calculated from the *F*-test. [a]$P < 0.05$, Statistically significant. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; SD: Standard deviation; NA: Not available.

Table 2 Analysis on gender and age of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/ General-HCC patients	PBC-series/ General-HCC patients	AIH-series/ PBC-series
Gender						
Actual number	Total: 38	Total: 50	Total: 16743			
Male	7 (18.4)	13 (26.0)	12025 (71.8)			
Female	31 (81.6)	37 (74.0)	4718 (28.2)	$P = 0.149$[1]	$P = 0.512$[1]	$P = 0.244$
Relative number	Total: 38	Total: 50				
Male	23.3 (61.3)	38.0 (76.0)				
Female	14.7 (38.7)	12.0 (24.0%)				
Age at HCC diagnosis	Total: 38	Total: 50	Total: 16743			
(mean ± SD)	(67.61 ± 8.58)	(68.54 ± 9.30)	NA			
< 40 s	0 (0)	2 (4.0)	761 (4.6)	NA	NA	$P = 0.410$
50 s	8 (21.0)	6 (12.0)	2818 (16.8)			($P = 0.614$)
60 s	16 (42.1)	21 (42.0)	6179 (36.9)			
70 s	9 (23.7)	14 (28.0)	5976 (35.7)			
< 80 s	5 (13.2)	7 (14.0)	1009 (6.0)			

The *P*-value above was calculated from the Mann-Whitney *U*-test and the *P*-value below, indicated in parentheses, was calculated from the *F*-test. [1]The *P*-value was calculated from the relative numbers. HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; SD: Standard deviation; NA: Not available.

population: interval between liver damage and HCC diagnosis, interval from HCC diagnosis to death, age at HCC diagnosis, serum-AFP levels, maximum tumor size and number of HCC loci. Because the patient sample size in each group was greater than 20, we chose to use *P*-values calculated from the asymptotic distribution. The total number of cases in each patient group did not include cases for which categorical data were unknown (Table 1).

The statistical analysis for survival among HCC patients with AIH and PBC was performed on a personal computer with the statistical package SPSS for Windows (version II, SPSS Inc., Chicago, IL, USA). Because there were too few published cases of HCC arising from AIH or PBC, however, differences in survival between patient groups could not be calculated.

RESULTS

The intervals between HCC diagnosis and death for HCC patients with AIH (14 ± 12 mo) and PBC (8.4 ± 14 mo) was notably shorter than among general HCC patients in Japan (77.5% 1-year survival, 52.5% 3-year survival, and 35.4% 5-year survival)[15]. As shown in Table 1, the survival interval for HCC patients with PBC was also significantly shorter than that for patients with AIH ($P = 0.047$)..

Among HCC cases associated with AIH, the actual male to female ratio was 7:31. Because AIH patients in Japan are predominantly female (7:1), the corrected risk ratio for HCC among male AIH patients was 1.6:1 relative to females, and the male to female ratio of the relative numbers was 23.3:14.7 (Table 2). The majority of Japanese PBC patients are also female, outnumbering

Table 3 Clinical status of reported cases of hepatocellular carcinoma associated with autoimmune hepatitis and primary biliary cirrhosis, compared to cases of general hepatocellular carcinoma in Japan

Clinical status	Compiled numbers (%)			*P*-values		
	HCC patients with AIH (AIH-series)	HCC patients with PBC (PBC-series)	General-HCC patients	AIH-series/General-HCC patients	PBC-series/General-HCC patients	AIH-series/PBC-series
History of blood transfusion	Total: 29	Total: 38	Total: 12602	$P = 0.040^a$	$P = 0.581$	$P = 0.041^a$
+	3 (10.3)	13 (34.2)	3633 (28.8)			
-	26 (89.7)	25 (65.8)	8969 (71.2)			
History of excessive alcohol intake	Total: 38	Total: 50	Total: 14694	$P = 0.812$	$P = 0.056$	$P = 0.352$
+	1 (2.6)	5 (10.0)	3271 (22.3)			
-	37 (97.4)	45 (90.0)	11423 (77.7)			
Co-infection	Total: 33	Total: 40	Total: 4121			
HBV (prior) +	2 (6.1)	10 (25.0)	2138 (51.9)	$P < 0.001$	$P < 0.001$	$P = 0.025$
HBV (prior) -	31 (93.9)	30 (75.0)	1983 (48.1)			
Co-infection	Total: 38	Total: 49	Total:16492			
HCV +	3 (7.9)	10 (20.4)	11488 (69.7)	$P < 0.001$	$P < 0.001$	$P = 0.044$
HCV -	35 (92.1)	39 (79.6)	5004 (30.3)			
Pathological findings of noncancerous lesion of the liver	Total: 31	Total: 44	Total: 4941	$P = 0.163$	$P = 0.007^b$	$P = 0.489$
NL, CH, LF	13 (41.9)	15 (34.1)	2691 (54.5)			
LC	18 (58.1)	29 (65.9)	2250 (45.5)			

HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NL: Normal liver; CH: Chronic hepatitis; LF: Liver fibrosis; LC: Liver cirrhosis.

males by 9:1. The relative risk ratio for HCC among males with PBC was 3.2:1 relative to females, and the male to female ratio of the relative numbers was 38:12 (Table 2). No significant differences in male to female ratios were noted between the three patient groups ($P = 0.149$, $P = 0.512$, $P = 0.244$, respectively).

Among the HCC cases associated with AIH, only three (10.3%) had a history of blood transfusions, while 13 (34.2%) of the cases with PBC had such a history. Among all Japanese patients with HCC, 3633 (28.8%) had a history of blood transfusions[15]. The proportion of HCC cases associated with AIH having a history of blood transfusions was significantly lower than that of the general HCC cases in Japan ($P = 0.040$), and the proportion of HCC cases associated with PBC having a history of blood transfusions was significantly greater than that of the HCC cases associated with AIH ($P = 0.041$, Table 3).

Similarly, only one case (3.1%) of HCC associated with AIH had a history of excessive alcohol intake, while five (20.0%) cases associated with PBC had such a history ($P = 0.352$, Table 3). Among all Japanese patients with HCC, 3271 (22.3%) had a history of excessive alcohol intake[15].

While prior infection with HBV was relatively rare among AIH patients (6.1%), it was much more prevalent among patients with PBC (25.0%, $P = 0.025$). Similarly, 7.9% of AIH patients tested positive for HCV, as compared to 20.4% of PBC patients ($P = 0.044$). The population of Japanese HCC patients without autoimmune liver disease had significantly higher rates of both HBV and HCV co-infection ($P < 0.001$, Table 3).

Among the HCC cases associated with AIH, 18/31 (58.1%) were found to have cirrhosis on examination of liver biopsy samples or resected samples at operation. In contrast, 29/44 (65.9%) of the HCC cases associated with PBC were found to have cirrhotic liver tissue. Within the general HCC population in Japan, 2250 of the 4941 cases for which liver specimens were available (45.5%) showed evidence of cirrhosis[15]. While the proportion of liver cirrhosis among HCC cases associated with PBC was significantly greater than that in the general HCC population in Japan ($P = 0.007$), no statistical significance in the prevalence of cirrhosis was found between AIH-associated HCC and general HCC patients ($P = 0.163$, Table 3).

The numbers and positive ratios of the AIH-series, PBC-series and general-HCC patients were 22/37 (59.5%), 34/47 (72.4%) and 10075/15831 (63.6%), respectively. No significant differences in positive ratios of serum-AFP were noted between the three patient groups ($P = 0.597$, $P = 0.216$, $P = 0.214$, respectively, Table 4). AFP levels at diagnosis were 2340.2 ng/mL (range 1-49100 ng/mL) among patients with AIH, and 854.2 ng/mL (range 4.2-14646 ng/mL) among patients with PBC. The maximum size of the primary hepatic tumor at diagnosis was 3.97 cm (range 1.0-10.0 cm) among patients with AIH and 3.51 cm (range 1.0-8.8 cm) among PBC patients (Table 4). Due to lack of available data, we could not compare serum AFP levels, tumor sizes and numbers of HCC loci between the autoimmune-associated HCC cases and the general HCC cases in Japan. However, we found that serum AFP level did not vary widely, and that maximum tumor size and number of HCC loci were considerably lower in patients with autoimmune liver disease than in general HCC patients (Table 4).

Among both the AIH and PBC patient groups,