Table 1 Background characteristics of patients with chronic hepatitis C

	Group 1 ($n = 5$) 24 weeks of IFN + DFPP	Group 2 ($n = 10$) 24 weeks of IFN + 24 weeks of Rib + DFPP	Group 3 ($n = 59$) 24 weeks of IFN + 24 weeks of Rib	Group 4 ($n = 15$) 48 weeks of IFN + 24 weeks of Rib + DFPP	Group 5 ($n = 30$) 48 weeks of PEG-IFN + 48 weeks of Rib + DFPP	Group 6 ($n = 74$) 48 weeks of PEG-IFN + 48 weeks of Rib	Statistical analysis
Sex (male/female)	4/1	8/2	33/26	11/4	21/9	46/28	NS, χ^2 (Yates' correction)
Age (years)	53 ± 13	53 ± 4	56 ± 9	50 ± 14	54 ± 8	55 ± 10	NS, ANOVA
Weight (kg)	59.0 ± 6.1	64.5 ± 7.3	62.1 ± 10.4	61.1 ± 10.4	68.9 ± 10.4	64.6 ± 10.6	NS, ANOVA
Liver biopsy							
Grading (0/1/2/3)	0/1/2/0	0/4/5/1	1/22/32/3	0/9/6/0	1/14/11/1	0/28/40/1	NS, χ^2 (Yates' correction)
Staging (0/1/2/3/4)	0/1/1/1/0	0/3/7/0/0	1/19/16/17/6	2/5/8/0/0	2/11/11/3/0	0/26/21/14/8	NS, χ^2 (Yates' correction)
Not done	2	0	1	0	3	5	
HCV-RNA (KIU/mL), *n* (%)							NS, χ^2 (Yates' correction)
100–500	1 (20)	2 (20)	22 (37)	5 (33)	10 (33)	24 (32)	
500 or above	4 (80)	8 (80)	37 (63)	10 (67)	20 (67)	50 (68)	
ALT (IU/L)	105.0 ± 67.9	85.7 ± 34.8	106.8 ± 72.2	105.1 ± 73.9	73.2 ± 46.7	87.5 ± 63.8	NS, ANOVA
Past IFN treatment, *n* (%)							NS, χ^2 (Yates' correction)
Naive	0 (0)	7 (70)	29 (50)	10 (66)	8 (27)	45 (61)	
Relapser or non-responder	5 (100)	3 (30)	28 (47)	4 (27)	22 (73)	29 (39)	
Unknown (relapser or non-responder)	0 (0)	0 (0)	2 (3)	1 (7)	0 (0)	0 (0)	

Data are presented as mean ± SD.

ALT, alanine aminotransferase; DFPP, double filtration plasmapheresis; IFN, interferon alpha-2b; NS, not significant; PEG-IFN, pegylated interferon alpha-2b; Rib, ribavirin.

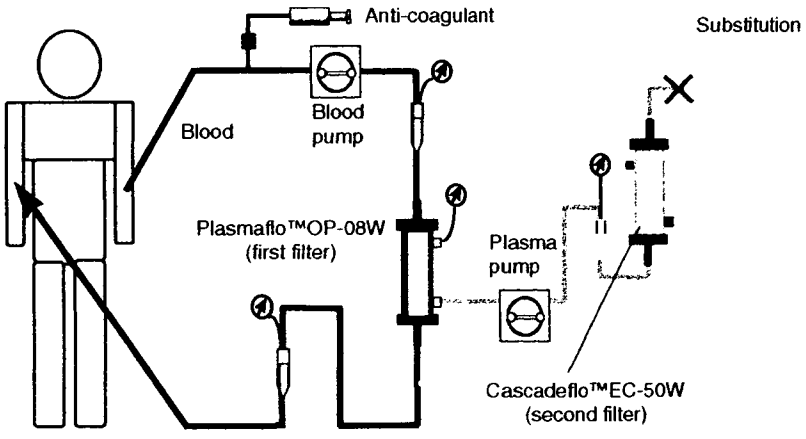

Figure 1 Schematic depiction of double filtration plasmapheresis (DFPP).

Performance of virus removal at second filter inlet and outlet

Plasma was collected from the inlet and outlet of the second filter during a session of DFPP, when the treated plasma volume reached half of the target quantity, and also when DFPP was completed. The changes in quantities of HCV-RNA were evaluated with these collected plasma samples.

Quantity of virus removed by a single session of DFPP

The quantity of virus removed by a single session of DFPP was computed based on two different hypotheses.

In the first hypothesis, in which the liver is assumed not to produce HCV, a one-compartment model was used to calculate the quantity of virus removed in a single session of DFPP.

$HCV\ RR = 1 - \exp(-SC \times V_{Pt}/V_P)$

$HCV\ RV = HCV\ RR \times C_{pre} \times V_P$

HCV RR: HCV removal ratio

HCV RV: HCV removed volume

V_P: total plasma volume (bodyweight × 1/13) × (1 − hematocrit value/100)

V_{Pt}: plasma volume treated by DFPP

C_{pre}: HCV-RNA quantity before DFPP

SC: sieving coefficient (set at 1)

In the second hypothesis, in which the liver is assumed to produce HCV, the quantity of virus removed in a single session of DFPP was calculated from the quantities of HCV-RNA in the serum collected before and after the first session of DFPP.

Viral reduction and viral response rate

In order to determine the viral reduction (Δlog), the quantity of HCV-RNA was determined and converted into a log of virus quantity at the beginning of treatment (A), as well as the virus quantity at each of the virus measurement points (B). The following was then calculated: $\Delta\log = \log A - \log B = \log (A/B)$. In groups 2, 3 and 4, viral reduction was determined by collecting blood, before, at 24 h, and at 2 weeks after the start of DFPP or IFN-α-2b therapy. In groups 5 and 6, blood was collected, before, at 24 h, and at 2 and 4 weeks after the start of DFPP or PEG-IFN-α-2b therapy.

Patients whose HCV-RNA became negative on the Amplicore HCV monitor qualitative method and whose transaminases were within the normal range at 24 weeks after the completion of IFN therapy were considered to exhibit a sustained viral response (SVR).

Evaluation of DFPP safety

The subjective and objective adverse events of DFPP were observed, and five clinical items were also measured; platelet count, lymphocyte count, hemoglobin levels, albumin levels, and fibrinogen levels. These were determined before the first session of DFPP, and before the successive DFPP on the second, third, fourth, fifth and sixth days, and at 2 weeks after the last session of DFPP.

Statistical analysis

Statistical analysis consisted of an analysis of variance for patient background factors, and a paired *t*-test for quantities of HCV-RNA at the second filter inlet during DFPP. The *t*-test was used for viral load reductions and the Fisher's exact test for viral response rates among the groups. The *t*-test was two-tailed, and differences of $P < 0.05$ were considered significant.

RESULTS

Combination therapy of IFN and DFPP

OF THE 193 cases examined, 133 received IFN therapies alone, while the remaining 60 underwent DFPP. SVR was not evaluated in the following patients. One patient in group 1 withdrew her consent before receiving DFPP. One patient in each of groups 2, 4, and 5 failed to come to the facility due to personal reasons. There were seven patients in group 3, three in group 4, one in group 5, and 10 in group 6 who terminated IFN therapies before the scheduled treatment was completed. Also, there was one patient in group 1, one in group 4, three in group 5, and six in group 6 who continued IFN therapies after the scheduled treatment was completed.

The number of DFPP sessions performed was five in six patients, four in 10, three in 42, two in one, and one in one. The time spent for DFPP treatment was 100–480 min (average, 194 ± 105 min).

Virus removal performance at second filter inlet and outlet in DFPP

The quantity at the second filter inlet was 1720 ± 1481 KIU/mL when the treated plasma volume reached half the target quantity, and 1520 ± 1057 KIU/mL when DFPP was completed. At the outlet, the quantity of HCV-RNA was below the detection limit in all but two cases in which the removal rate was 99.98% or higher.

Quantity of virus removed by a single session of DFPP

The total plasma volume of patients undergoing DFPP ranged from 1200 mL to 4168 mL (average, 2945 ± 544 mL). The average plasma volume by a single session of DFPP was 46.7 ± 8.9 mL/kg bodyweight. The total treated plasma volume by DFPP ranged from 2030 mL to 4650 mL (average, 3161 ± 420 mL).

From the standpoint of the first hypothesis, in which the liver is assumed not to produce HCV $(4.69 \pm 4.50) \times 10^9$ IU HCV was removed in a single session of DFPP (HCV RV) and the HCV removal ratio (HCV RR) was 66.3 ± 7.1%. For the second hypothesis, which assumes that the liver produces HCV, the quantities of HCV-RNA in sera were compared before and after a single session of DFPP. The quantity of HCV-RNA ranged from 130 KIU/mL to 13 853 KIU/mL (average, 2392 ± 2139 KIU/mL) before DFPP, but after DFPP the quantity fell significantly to 27–4699 KIU/mL (average, 1494 ± 969 KIU/mL) ($P < 0.001$), showing that a single session of DFPP removed $(3.08 \pm 5.81) \times 10^9$ IU HCV and that the removal ratio was 26.1 ± 36.4%

Viral reduction effects in combined treatment with DFPP

All cases in groups 2 and 4 receiving DFPP plus IFN-α-2b and ribavirin showed viral load reduction significantly larger at 24 h after the start of treatment than in group 3 receiving non-DFPP ($P < 0.001$). At 2 weeks after the start of treatment, the viral load reduction in the groups undergoing DFPP exceeded 2 log units and was significantly larger than the reduction in the groups undergoing non-DFPP ($P = 0.034$). The viral load reduction for patients re-treated with DFPP who were either relapsers or non-responders following previous IFN therapy was (1.62 ± 0.46) log at 24 h after the start of treatment, and (2.88 ± 0.78) log at 2 weeks. These values were significantly larger than (0.79 ± 0.52) log at 24 h and (1.45 ± 0.81) log at 2 weeks in Group 3 without DFPP ($P = 0.007$ and $P < 0.001$, respectively) (Fig. 2).

In Group 5 treated with DFPP plus PEG-IFN-α-2b and ribavirin, the viral load reduction 2 weeks after the start of treatment was (1.48 ± 0.80) log in all cases (1.58 ± 0.80) log in the re-treated patients, and (1.20 ± 0.78) log in the former non-responders. All of these values were larger than the corresponding values in group 6 without DFPP. In addition, the reduction in group 5 at 4 weeks after the start of treatment in these cases was (2.43 ± 1.07) log (2.47 ± 1.11) log and (2.13 ± 0.71) log, respectively, and exceeded 2 logs in group 6, in which the reduction was (1.52 ± 1.08) log in the re-treated patients ($P = 0.010$) and (1.46 ± 1.17) log in the-non-responders (Fig. 3).

Sustained virus response rate

In patients treated with IFN-α-2b, SVR was seen in one of three cases in group 1, three of nine cases in group 2, nine of 52 cases in group 3, and all of 10 cases in group 4. In patients treated with PEG-IFN-α-2b, SVR was seen in 17 of 24 (70.8%) in group 5, and in 29 of 58 (50.0%) in group 6 ($P = 0.094$). In the re-treated patients, SVR was seen in 14 of 18 (77.8%) in group 5, and in 11 of 22 (50.0%) in group 6, and in non-responders, in five of seven (71.4%) in group 5, and in two of seven (28.6%) in group 6 (Fig. 4).

Safety of DFPP treatment

When DFPP treatment was conducted, 23 of 60 cases (38.3%) experienced some adverse events with 32 reported incidents in total (Table 2). A drop in blood

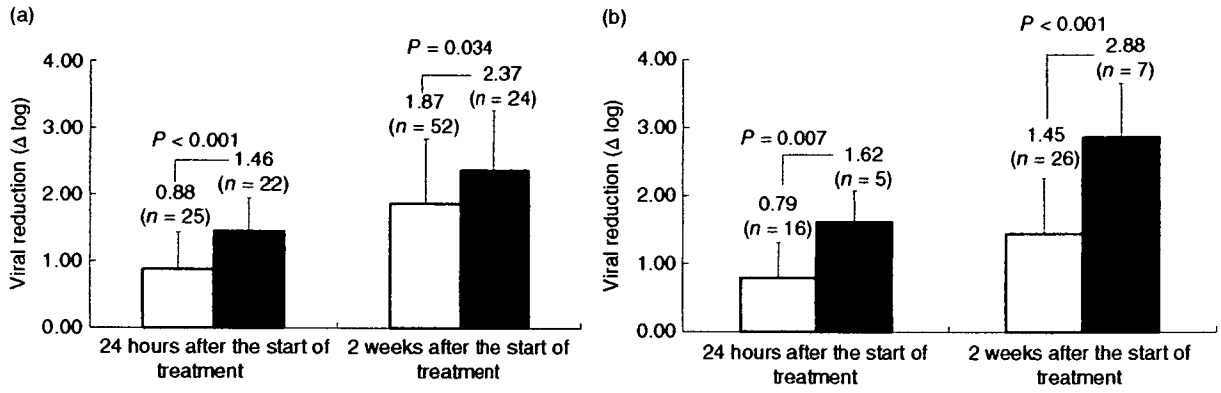

Figure 2 Viral reduction in groups with interferon alpha-2b and ribavirin, with and without double filtration plasmapheresis (DFPP). (a) Viral reduction in all patients. , Group 3 (all patients); ■, groups 2 and 4 (all patients). (b) Viral reduction in re-treated patients. , Group 3 (re-treated patients); ■, groups 2 and 4 (re-treated patients). Data are expressed as mean ± SD.

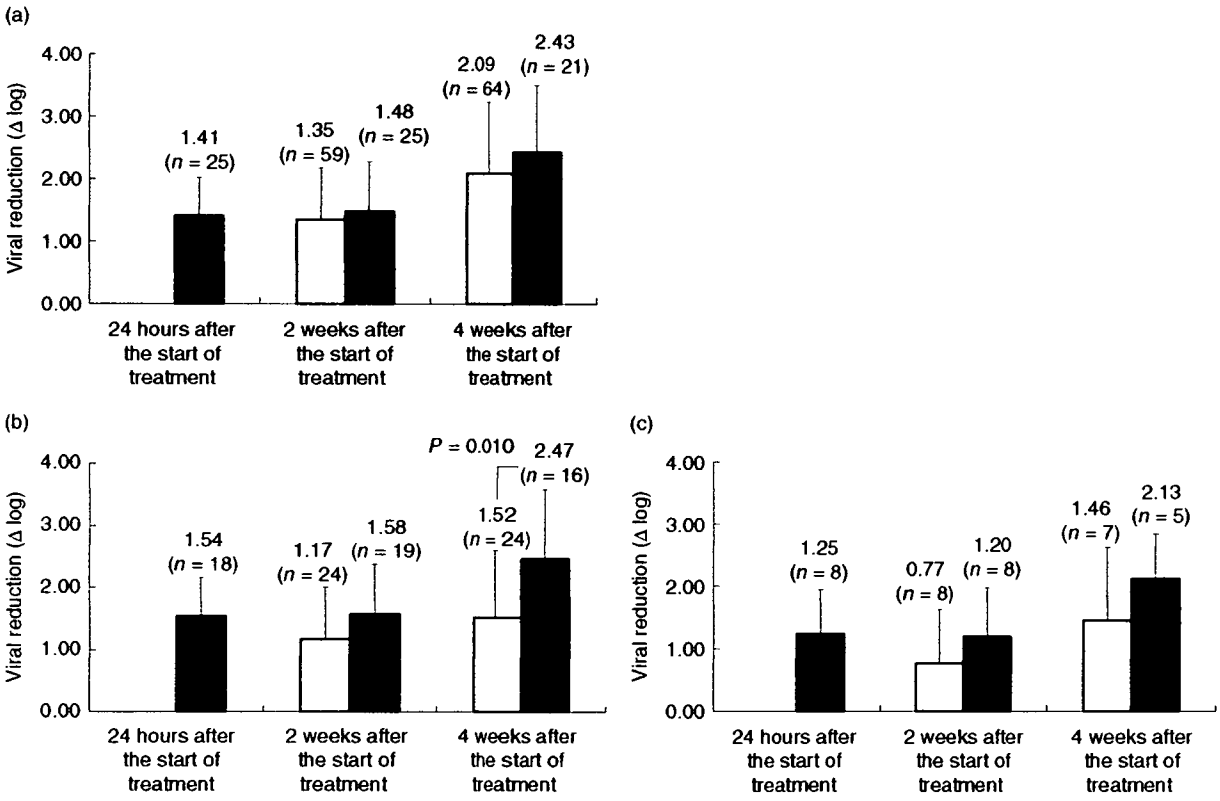

Figure 3 Viral reduction in groups with pegylated interferon alpha-2b and ribavirin, with and without double filtration plasmapheresis (DFPP). (a) Viral reduction in all patients. , Group 6 (all patients); ■, group 5 (all patients). (b) Viral reduction in re-treated patients. , Group 6 (re-treated patients); ■, group 5 (re-treated patients). (c) Viral reduction in non-responders. , Group 6 (non-responders); ■, group 5 (non-responders). Data are expressed as mean ± SD.

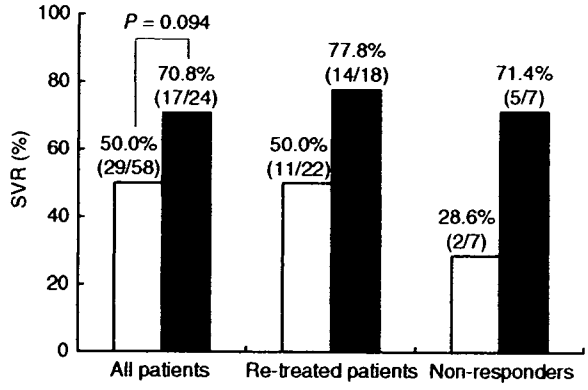

Figure 4 Sustained virus response rates (SVR) in patients treated with pegylated interferon alpha-2b and ribavirin, with and without double filtration plasmapheresis (DFPP). , Group 6; ■, group 5.

pressure was observed in four cases, but recovered after giving intravenous 100–200 mL normal saline solution. One case lost consciousness, but recovered after 2–3 min by Ambu pressure and oxygen inhalation and giving atropine sulfate and intravenous metoclopramide. Because the drop in blood pressure and loss of consciousness were temporary, all four patients continued to receive DFPP onwards. Minor disorder was found in 10 cases, but was temporary and recovered without any treatment. All other adverse events were also temporary.

Figure 5 demonstrates changes in the platelet count, lymphocyte count, hemoglobin levels, albumin levels, and fibrinogen levels. The platelet count and lymphocyte count fell temporarily during DFPP, but recovered to initial levels within 2 weeks in all cases. There were no changes in hemoglobin and albumin levels. The fibrinogen levels fell significantly from 234 ± 52 mg/dL to 142 ± 29 mg/dL ($P < 0.001$) on the day after DFPP (removal rate = 37.8%). This reduction continued during the period of DFPP, but recovered to initial levels within 1 week after the completion of DFPP. There were no bleeding or other adverse events sometimes accompanying a decline in fibrinogen levels.

Table 2 Adverse events during double filtration plasmapheresis treatment

Symptom	No. cases	No. incidents
Minor disorder	10	11
Decline of blood pressure	4	5
Loss of consciousness	1	1
Fever	2	2
Chills	2	2
Vomiting	2	2
Nausea	5	6
Pain in right brachial	1	1
Vagal reaction	2	2

DISCUSSION

DOUBLE FILTRATION PLASMAPHERESIS has been applied to many diseases and its safety has been established.[22,23] In the present study, DFPP was applied to chronic hepatitis C patients in combination with IFN therapy, and the adverse events were all those characteristic of DFPP, such as minor disorder, reduced blood pressure and nausea. It is reported that chronic hepatitis C patients experience a decline in the number of platelets or lymphocyte count, and that giving IFN can induce further reductions.[24] With DFPP, only a temporary decline in these two levels was noted. Because fibrinogen has a molecular weight of 340 000 and some of this can be removed (removal rate: 37.8%), there was a case in the present study in which fibrinogen levels fell below 100 mg/dL but recovered to the initial levels within 1 week after completion of DFPP. However, none of the cases in this study experienced bleeding or other serious adverse events. This demonstrates that DFPP can be used safely in combination with IFN therapy to treat chronic hepatitis C.

In order to assess the efficacy of virus removal, HCV-RNA load was recorded at the inlet and outlet of the second filter, when treated plasma volume reached half the targeted volume, and when DFPP was completed. As a result, the filter removed at least 99.98% of the virus. This would indicate that almost all of the HCV with an average particle diameter of 55–65 nm[25] was trapped by the second filter with an average pore size of 30 nm[26] Moreover, because the virus quantity fell below the detection limit in almost all cases, it is certain that the second filter efficiently removed the virus throughout DFPP.

The quantity of virus removed by a single session of DFPP was assayed in consideration of two different hypotheses. In the first hypothesis that the liver does not produce HCV, a computation based on a one-compartment model yielded $(4.69 \pm 4.50) \times 10^9$ IU as the quantity of virus removed by DFPP and 66.3 ± 7.1% as its removal ratio. Under these circumstances, new viruses are produced in the liver even after viral removal by DFPP, because the liver produces 10^{12} HCV per day.[27]

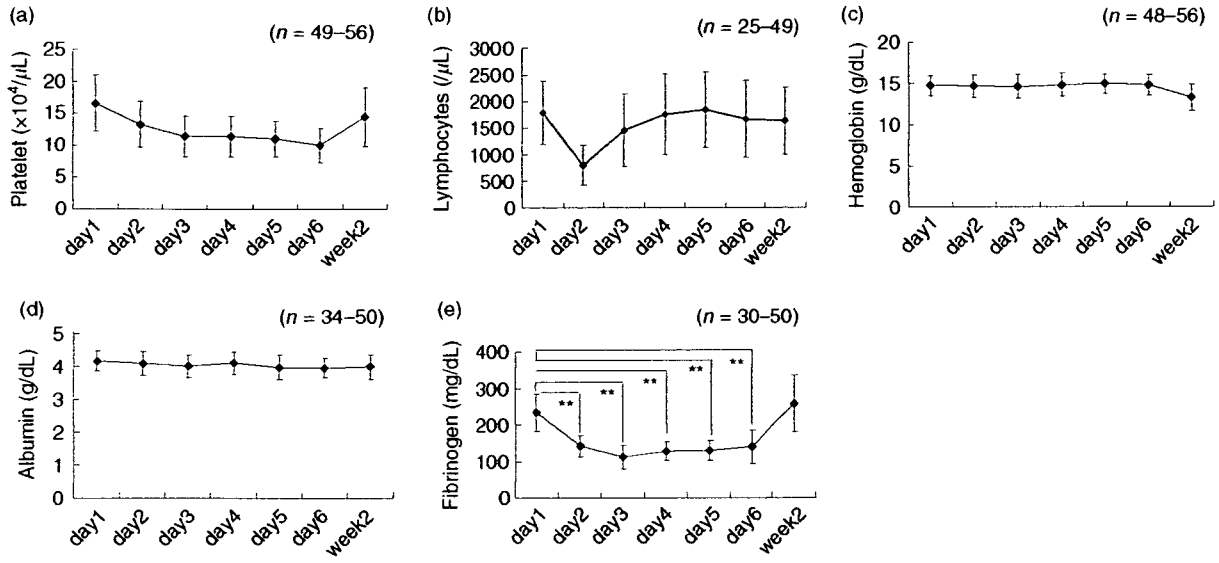

Figure 5 Changes in laboratory data during interferon treatment with double filtration plasmapheresis (DFPP). Data are expressed as mean ± SD. $^{**}P < 0.001$.

In the second hypothesis that the liver can produce HCV, the quantity of virus removed by DFPP was calculated from actual clinical results. The quantity of HCV-RNA in the serum significantly decreased from an average of 2392 ± 2139 KIU/mL before DFPP to 1494 ± 969 KIU/mL after DFPP ($P < 0.001$). DFPP removed $(3.08 \pm 5.81) \times 10^9$ IU of the virus and the removal ratio was 26.1 ± 36.4%, despite the virus being newly produced by the liver.

Moreover, the present study demonstrated that the viral load reduction at 24 h after the start of IFN-α-2b therapy was significantly greater in the groups undergoing DFPP combined with IFN therapy than in non-DFPP groups ($P < 0.001$, Fig. 2a; $P = 0.007$, Fig. 2b). The underlying mechanism is not known; however, there may be several explanations for the significant reduction with the combination DFPP treatment. One explanation is that the reduced viral return to the infected liver by combination DFPP treatment may have a favorable effect on the IFN efficacy. Another possibility is that DFPP treatment changes the viral nature in the blood, and affects the efficacy. In chronic hepatitis C patients, there are two fractions of HCV particles in the blood according to its buoyant density which relate viral titer or disease states.[28–30] One is a high-density fraction in which HCV particles form an immunocomplex with immunoglobulin G (IgG), the other is a low-density fraction where HCV particles bind to low-density lipoprotein (LDL). Removal of circulating HCV by DFPP treatment decreases the amount of the high-density fraction of HCV particles, and may be associated with the IFN response, as we reported that the lower ratio of the high-density fraction of HCV was associated with the response to interferon treatment.[18–20]

The quantity of HCV-RNA showed that DFPP combined with IFN therapy reduced viral numbers at all samplings (i.e. at 24 h, 2 weeks, and 4 weeks after the start of IFN therapy). In particular, the groups receiving DFPP combined with IFN-α-2b and ribavirin, or PEG-IFN-α-2b and ribavirin showed a 2 log or greater viral load reduction at 2 weeks or 4 weeks after the start of IFN therapy, respectively. Davis reported that an early viral reduction of 2 logs or more is important in removing the virus.[31] The use of DFPP at the start of IFN therapy may constitute a crucial treatment for viral removal.

DFPP was effective in non-responders who had previously received IFN therapy. Moreover, in the groups treated with PEG-IFN-α-2b therapy alone, non-responders showed a viral load reduction of (1.46 ± 1.17) log at 4 weeks after the start of treatment, whereas the reduction was (2.13 ± 0.71) log in the groups with DFPP. This difference was reflected in the SVR, which was two of seven cases (28.6%) in patients without DFPP and five of seven cases (71.4%), suggesting that forcible removal of the virus by DFPP can make

non-responders responsive to IFN therapy in a short period of time.

The groups of treatment in the present study were selected by patients' wishes, and thereby the patients were not randomly assigned to the groups. Nevertheless, there was little difference in patient clinical background factors (Table 1). Significant difference of rate of SVR between IFN with and without DFPP was not statistically obtained in this study using a limited number of patients. However, DFPP is assumed to provide effective treatment even for chronic hepatitis C patients resistant to IFN therapy. Further study is clearly necessary to determine the effectiveness of this combination therapy, and to understand the mechanisms of virus production and elimination by DFPP.

ACKNOWLEDGMENT

WE THANK ASAHI Kasei Medical, Tokyo, Japan, for technical support.

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Int Urol Nephrol (2007) 39:461–463
DOI 10.1007/s11255-006-9006-8

CASE REPORT

Reactivation of hepatitis in a bladder cancer patient receiving chemotherapy

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Received: 16 March 2006 / Accepted: 18 April 2006 / Published online: 14 December 2006

Abstract Reactivation of hepatitis is a serious complication of chemotherapy in hepatitis B virus (HBV) carriers. There are many reports of this in lymphoma patients but few in urological cancer patients. A 59-year-old woman with bladder cancer who was an HBV carrier developed severe liver dysfunction after 2 cycles of chemotherapy. The diagnosis was reactivation of hepatitis. She improved with administration of lamivudine with a steroid and is currently well without disease. Care should be taken about the risk of reactivation when performing chemotherapy in HBV carriers and prophylaxis by lamivudine should be considered.

Keywords Hepatitis B virus · Chemotherapy · Reactivation · Lamivudine

Introduction

Reactivation of hepatitis is a serious complication of chemotherapy in hepatitis B virus (HBV) carriers. There have been a number of cases reported during treatment of lymphoma; however, only one case has so far been reported for urological cancer treatment [1]. We herein report a case of chemotherapy-induced hepatitis flare in a patient with bladder cancer.

A 59-year-old woman was diagnosed as having infiltrating bladder carcinoma with metastasis to local lymph nodes. She was an HBV carrier but had no active hepatitis and a normal alanine aminotransferase level (ALT, normal < 40 IU/l), positive HBs Ag, positive anti-HBe Ab, positive serum HBV-DNA (4.9×10^6 copies/ml, normal $< 4 \times 10^2$ copies/ml). Following cystectomy she received chemotherapy consisting of methotrexate, epiadriamycin and cisplatin. At the end of the second cycle of chemotherapy, just after the withdrawal of 4 mg/day dexamethazone for antiemesis, she presented with general fatigue and appetite loss. Laboratory tests showed ALT elevated to 2,000 IU/l (Fig. 1). Although her serum HBV-DNA level decreased to 4.7×10^2 copies/ml, she was diagnosed as having reactivation hepatitis because a thorough evaluation did not indicate any other cause for liver dysfunction. She was started on lamivudine at 100 mg/day with 500 mg of steroid therapy for 3 days. One week later she developed reversible posterior leukoencephalopathy syndrome, and required an anticonvulsion agent and respiratory care for 1 month. She improved 3 months later; ALT

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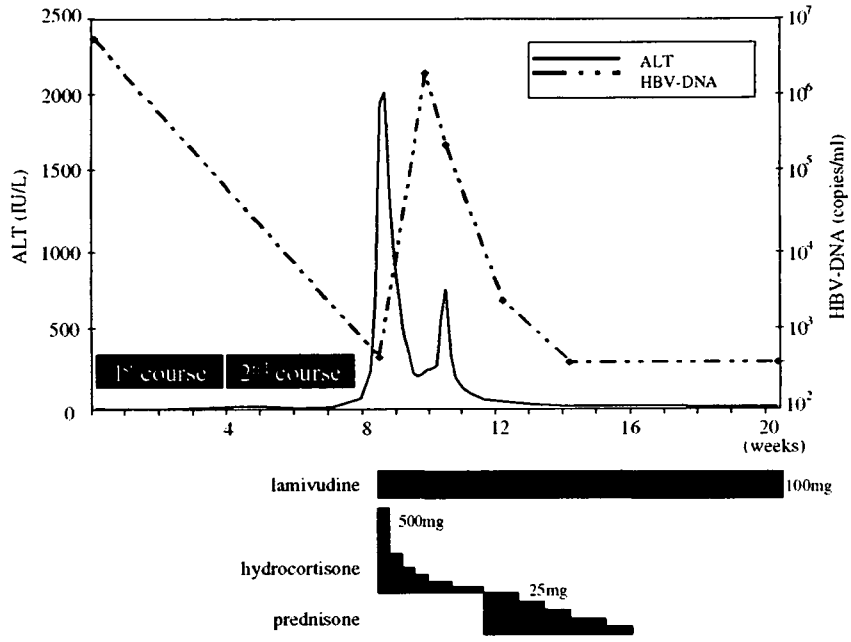

Fig. 1 The time courses of ALT and HBV-DNA

normalized and serum HBV-DNA was undetectable when lamivudine was stopped. After the discontinuance of chemotherapy she has been well without evidence of cancer recurrence or hepatitis for 2 years of follow-up.

Discussion

Reactivation of HBV is well known in lymphoma patients undergoing cytotoxic chemotherapy. The mechanism of flare in HBV carriers has not been clearly elucidated, though a possible mechanism is that increased HBV-infected hepatocytes due to immunosuppressive agents, which are disintegrated by the attack of restored activated T-cells after the withdrawal of the agents [2].

The frequency of HBV reactivation in HBs Ag-positive lymphoma patients receiving chemotherapy was reported to range from 15% to 20%. The HBV-DNA usually rises and drops rapidly soon after ALT elevation, so the true incidence of HBV reactivation might be underestimated in retrospective studies. In fact, we did not detect a rise of HBV-DNA during the clinical course. Patients with positive HBV-DNA have a risk for flare-up. In addition, the use of steroids was reported to be a risk for reactivation. Upon withdrawal of steroids, there is an intense rebound in cytotoxic T-cell function that coincides with a surge in serum ALT and decreases in the levels of HBs Ag and HBV-DNA [3].

Lamivudine inhibits reverse transcription activity and DNA synthesis, is well tolerated and the adverse effects are mild. However, long-term lamivudine use is associated with the development of lamivudine-resistant mutant strains of HBV. Despite this risk, prophylaxis against chemotherapy-induced reactivation is recommended [4].

There has hitherto been only one report of HBV reactivation in urological cancer chemotherapy. However, as our case demonstrates, this remains a possibility and care should be taken about reactivation when performing chemotherapy in HBV carriers; monitoring HBV-DNA is mandatory and prophylaxis by lamivudine should be considered.

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Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 2, pp. 376–380, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.03.042

CLINICAL INVESTIGATION **Liver**

INTERCEPTING RADIOTHERAPY USING A REAL-TIME TUMOR-TRACKING RADIOTHERAPY SYSTEM FOR HIGHLY SELECTED PATIENTS WITH HEPATOCELLULAR CARCINOMA UNRESECTABLE WITH OTHER MODALITIES

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Purpose: To assess the clinical outcome of intercepting radiotherapy, in which radiotherapy is delivered only when a tumor in motion enters a target area, using a real-time tumor-tracking radiotherapy (RTRT) system for patients with hepatocellular carcinoma who were untreatable with other modalities because the tumors were adjacent to crucial organs or located too deep beneath the skin surface.

Methods and Materials: Eighteen tumors, with a mean diameter of 36 mm, were studied in 15 patients. All tumors were treated on a hypofractionated schedule with a tight margin for setup and organ motion using a 2.0-mm fiducial marker in the liver and the RTRT system. The most commonly used dose of radiotherapy was 48 Gy in 8 fractions. Sixteen lesions were treated with a BED_{10} of 60 Gy or more (median, 76.8 Gy).

Results: With a mean follow-up period of 20 months (range, 3–57 months), the overall survival rate was 39% at 2 years after RTRT. The 2-year local control rate was 83% for initial RTRT but was 92% after allowance for reirradiation using RTRT, with a Grade 3 transient gastric ulcer in 1 patient and Grade 3 transient increases of aspartate amino transaminase in 2 patients.

Conclusions: Intercepting radiotherapy using RTRT provided effective focal high doses to liver tumors. Because the fiducial markers for RTRT need not be implanted into the tumor itself, RTRT can be applied to hepatocellular carcinoma in patients who are not candidates for other surgical or nonsurgical treatments. © 2007 Elsevier Inc.

Radiotherapy, Liver, Hepatocellular carcinoma, Real-time tumor-tracking radiotherapy.

INTRODUCTION

There are a number of nonsurgical local treatment techniques for the ablation of hepatocellular carcinoma (HCC), including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and cryosurgery (1). These techniques require direct insertion of a needle or probe into the tumor mass. However, with HCC at deep locations, such as the top of the dome, near the inferior vena cava, or near the main portal vein, a needle or probe often cannot be inserted at the proper position. Transarterial embolization (TAE) is applicable only when one can identify the feeding artery, which is often difficult (2).

Radiotherapy has been a palliative treatment for patients with unresectable advanced HCC, but conventional radiotherapy is limited by the liver's low tolerance to large volumes of irradiation (3). Both focal radiotherapy using narrow-beam X-ray and particle therapy are expected to be useful for reducing radiation-induced liver damage (RILD) (4). When the tumor is close to the gastrointestinal (GI) tract, radiation-induced GI ulcer is a dreadful complication (5). Moreover, it is hard to increase the dose to the HCC when the tumor is in that position, owing to the large respiratory movement of the liver. In particle therapy, such as proton and carbon ion treatment, respiratory gating systems have been used to reduce the volume of normal tissue in the irradiated volume. As a result, the dose to the GI tract might be reduced in the particle therapy (6, 7).

In 1999 we began using a real-time tumor-tracking radiotherapy (RTRT) system to increase the accuracy of the nonsurgical treatment of tumors in motion (8). This has made intercepting radiotherapy possible for tumors in motion, whereby the tumor is irradiated only when it enters a target area, with a certain amount of permitted dislocation. After developing a technique to percutaneously insert a 2.0-mm gold

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Supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, and Technology in Japan (No. 18209039, No. 17016002).

Conflict of interest: none.

Received Oct 30, 2006, and in revised form Feb 27, 2007. Accepted for publication March 2, 2007.

fiducial marker into the liver and to confirm its localization stability (9), we suggested that intercepting radiotherapy using RTRT can be a radical radiotherapy for primary HCC (10). Because the fiducial marker does not need to be inserted directly into the tumor when RTRT is used, this method is applicable to more patients than is the case with percutaneous focal ablation techniques, such as RFA and cryosurgery. However, we have restricted the indication of RTRT to patients who were not eligible for other nonsurgical treatment techniques. In the present study, the outcomes of patients treated with the RTRT technique in the last 5 years were retrospectively analyzed to determine its proper indications for HCC.

METHODS AND MATERIALS

The focus of this study was on primary HCC diagnosed by dynamic computed tomography (CT) with the aid of serum tumor marker, according to the noninvasive Barcelona criteria (11). Patients were candidates if they were not eligible for any other treatment, such as surgery, RFA, PEI, and TAE. They were required to be 80 years old or younger and to have a Karnofsky performance status of 70% or more, as well as a liver function equivalent to Class A or B in the Child classification. Patients were excluded if they had uncontrolled ascites, obstructive jaundice, active gastroenteric bleeding, or a tendency to bleed. Patients who had tumor thrombosis of the portal vein or extrahepatic active metastatic disease on imaging examination were also excluded.

Multidetector CT was taken with a breath hold at the end of the expiratory phase of normal breathing. The slice thickness and interval were 2 mm. Gross tumor volume (GTV) was chosen to be compatible with the enhanced area in the early arterial phase of dynamic CT. Clinical target volume (CTV) was GTV plus a 5-mm margin three-dimensionally; thus the CTV diameter was 10 mm larger than the GTV. Planning target volume (PTV) was CTV plus a 5-mm margin three-dimensionally in principle. Modification of the PTV margin from 5 to 10 mm was allowed for the craniocaudal direction when no critical organs, such as the duodenum, were close to the edge of the PTV.

Dose–volume constraints were made for liver, lung, and GI tract according to previous reports and to our own preliminary studies. The maximum tolerable dose (MTD) to the liver adopted in this study was 30 Gy, using a 2-Gy daily dose for total liver volume (12). The biologic effective dose with an α/β ratio of 2 (BED_2) of the MTD was 60 Gy. The volume of liver that could receive 40 Gy in 20 fractions was assumed to be 30% of the whole liver in a dose–volume histogram. Alteration of dose fractionation was allowed to reduce the daily dose to the GI tract. The MTD of the GI tract was 40 Gy in 20 fractions, or BED_2 of 80 Gy. Based on these considerations, the total doses and fractionation schedules are listed in the study protocol as guidelines (Table 1). For example, if the tumor is >5 cm and the edge of the organ at risks is less than 1 cm, only 48 Gy in 8 fractions can be used. If the tumor is less than 3 cm and the edge of the GTV is 3 cm or more distant from the organ at risks, 20 Gy in one session or some other schedule can be used. This schema was developed to allow clinical staff members to select schedules based on the preliminary results of dose–volume statistics. Because of the insufficient data on the MTD, several dose schedules were allowed to be chosen.

Megavoltage X-rays (6, 10 MV) from a linear accelerator with five to seven single isocenter, non-coplanar ports were used. The dose was prescribed at the isocenter, giving 80% of the isocentric dose to cover PTV. A round, 2-mm gold marker was implanted near the tumor, within 3 cm from the isocenter of the GTV in principle. The reliability of the inserted marker as the GTV surrogate has already been reported (9). In short, the relationship between the gravity center of the liver and the marker was reproducible in the sequential CT examination for more than 1 month. Two sets of fluoroscopic cameras in the treatment room were used for the real-time recognition of the marker every 0.033 s during the delivery of the therapeutic beam. The therapeutic beam was gated to irradiate the tumor only when the marker was within 2.0 mm of the planned coordinates in lateral, anteroposterior, and craniocaudal directions.

The patients were followed up with a physical examination, blood collection, and either CT or magnetic resonance imaging every 3 months for 1 year and every 4–6 months thereafter by radiation oncologists with the help of hepatologists.

The Kaplan-Meier method was used to calculate the overall survival, local control, and intrahepatic control rates, in which any new lesions were counted as a failure. Adverse effects were scored according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.

RESULTS

From 2001 to 2004, 18 lesions of 15 patients were entered into this study. The patients were aged 54–73 years (median, 57 years). Hepatic function before radiotherapy was classified as Child class A, B, and C in 12, 3, and 0 patients, respectively. Five patients suffered from hepatitis B virus, 9 from hepatitis C virus, and 1 from alcoholic hepatitis. Tumors were located at the hepatic segments S1, S2, S6, S7, and S8 according to the Couinaud classification (13) in 3, 4, 3, 1, and 7 patients, respectively. The tumor diameter ranged from 15 to 52 mm (mean, 36 mm; standard deviation, 14 mm).

The reasons for RTRT were as follows: too close to the portal vein or inferior vena cava for other treatments, such as RFA or PEI, in 4 patients; located at the hepatic dome (S8) and far from other treatments in 3 patients; residual disease after other treatment in 2 patients; and coexisting illness in 3 patients.

The prescribed doses and fractionation used in the actual study are shown in Table 1. Various schedules were used according to the size and position of the tumor to restrict the dose to the critical organ. The most common dose in this study was 48 Gy in 8 fractions. The biologic effective dose with an α/β ratio of 10 (BED_{10}) was distributed from 39 to 106 Gy without consideration for cell proliferation. Seventeen lesions were treated with a BED_{10} of $\geq$50 Gy, and 16 lesions were treated with a BED_{10} of $\geq$60 Gy or more (median, 76.8 Gy).

With a mean follow-up period of 20 months (range, 3–57 months), the overall survival rate was 44% (standard error [SE] 14%) at 21 months after RTRT (Fig. 1). Rates of 1- and 2-year actuarial survival after RTRT were 79% and 44%, respectively. The local control rate within the CTV was 83% (SE 11%) at 30 months after RTRT. The intrahepatic control rate was 34% (SE 13%) at 10 months and 17% at 2 years after RTRT (Fig. 1). There were two local failures. One patient with a 20-mm tumor was treated with 48 Gy in 8 fractions in 2 weeks and relapsed at 8 months from the

Table 1. Doses and fractionations used in the intercepting radiotherapy

			Tumor size (GTV) (cm)			Distance from OAR (cm)[†]		
Dose (Gy)/fraction	*n*	BED_2/BED_{10} (Gy)*	<3	3–5	>5	<1	1–3	>3
20/1	1	220/60	1	—	—	—	—	1
48/4	1	336/106	—	1	—	—	—	1
40/4	3	240/80	1	1	1	—	1	2
48/8	7	192/76.8	1	5	1	1	4	2
40/8	2	140/60	—	2	—	—	2	—
40/16	1	90/50	—	1	—	—	1	—
Out of protocol	3	37/8, 30/10, 40/20+36/8	—	2	1	2	1	—

Abbreviations: GTV = gross tumor volume; OAR = organ at risk.
Tumor sizes and distances from the organ at risk of the patients treated are shown for each dose/fractionation schedule.
* Biologic equivalent dose, assuming an α/β ratio of 2 and 10 for BED_2 and BED_{10}, respectively.
† Minimum distance between the edge of clinical target volume and OAR.

margin of the tumor. The patient was treated by TAE afterward and survived for 21 months. The other patient, with a 15-mm tumor, was treated with 20 Gy in one session and relapsed at 10 months from the inside of the GTV. The latter was treated again with RTRT, and the tumor was controlled for 8 months thereafter. No other patients received transarterial chemoembolization or local ablation in combination with RTRT. In cases in which we allowed reirradiation for the relapsed tumor as a part of the treatment, the local control rate of the radiotherapy was 92% at 30 months. The 2- and 5-year actuarial survival rates after the initial treatment for HCC were 93% and 52%, respectively.

A symptomatic complication due to the insertion of the fiducial marker occurred in 1 patient, who experienced transient bile ductal bleeding and inflammation. An adverse reaction due to radiation was seen in 2 patients. A transient gastric ulcer in a patient with a 50-mm tumor adjacent to the stomach was salvaged by emergency endoscopic treatment (Grade 3 adverse effect), and the patient has been alive with no evidence of disease at 58 months. Radiation pneumonitis in a patient with a 45-mm tumor at the hepatic dome without the requirement of medication (Grade 1 adverse effect) was observed at 4 months after RTRT. No radiologic change was found in the follow-up CT taken at 20 months after RTRT.

There were no encephalopathy and ascites in the patients without tumor progression. Changes in transaminase levels after RTRT were available in 10 patients and are shown in Fig. 2. Several patients experienced increased transaminase at the subacute phase after RTRT transiently. There was no Grade 4 toxicity of liver function due to radiation, and there were two Grade 3 toxicities of transient elevation of aspartate amino transaminase (elevation at least 5 to 10 times the upper limit of normal).

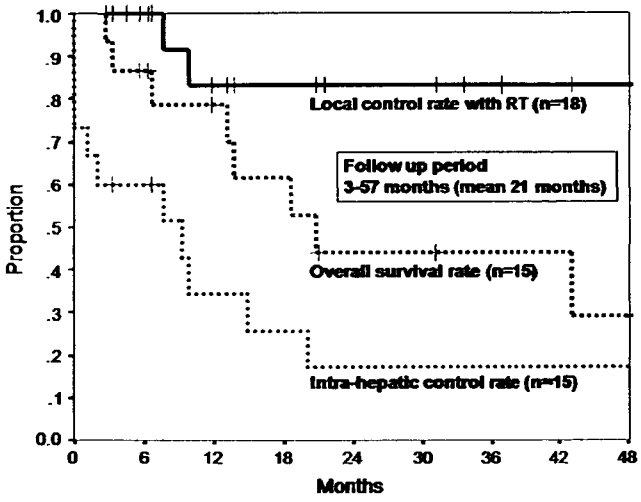

Fig. 1. Kaplan-Meier curves of overall survival and intrahepatic control rates for 15 patients with hepatocellular carcinoma (HCC) and local control rate with reirradiation for 18 HCC in the 15 patients. RT = radiotherapy.

DISCUSSION

Localized X-ray radiotherapy has been shown to achieve excellent local control rates with lower rates of radiation-induced liver dysfunction compared with conventional radiotherapy (4). Park *et al.* (14) reported a dose–response relationship in the local control rate of primary HCC. More recently, Park *et al.* (15) reported achieving an objective tumor response in 39 of 59 patients (66.1%), with complete response

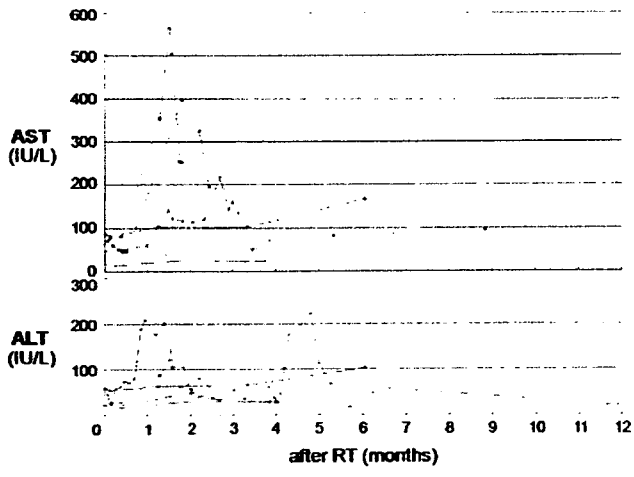

Fig. 2. Changes in transaminases. Alanine amino transaminase (ALT) and aspartate amino transaminase (AST) levels after real-time tumor-tracking radiotherapy (RT) in 10 patients.

in 5 patients and partial response in 34 patients using localized X-ray radiotherapy. The BED_{10} >50 Gy had a significantly better response rate (complete or partial response) of 72.8% compared with 46.7% with BED_{10} ≤50 Gy (p = 0.0299). The present study used BED_{10} >50 Gy in 17 of 18 lesions and showed local control rates of 83% after initial RTRT and 92% at 30 months when we included reirradiation with RTRT for the local relapse. Considering the smaller margin for CTV in RTRT compared with that in radiotherapy without a real-time tracking system, we can say that RTRT can accurately treat liver tumors in motion. The dose specification used in the present study was 80–90% at the periphery of the PTV. More accurate dose specification should be used in future studies.

Treatment of HCC by conventional radiotherapy is difficult owing to the adverse hepatic events that may be caused by radiation. Furuse *et al.* (3) observed Grade 3 toxicity in 18 of 46 patients (39.1%) with HCC within 3 months after radiotherapy of 50 Gy in 5 weeks, and Grade 4 toxicity in 11 of 33 patients (33.3%) thereafter, using an arrangement of two or three coplanar beams. Yang *et al.* (5) found hematologic toxicity in 34.6% and hepatobiliary complications in 26% of 153 patients with HCC treated with radiotherapy. Dawson *et al.* (16) carefully estimated the volume effect of the liver from more than 180 patients and found that RILD was not evident in patients with a mean liver dose of <31 Gy. They estimated that if <25% of the normal liver is treated with radiotherapy, then there may be no upper limit on the dose associated with RILD (17). In their estimation, the liver doses associated with a 5% risk of RILD for uniform irradiation of one third, two thirds, and the whole liver were 90, 47, and 39 Gy, respectively, with a daily dose of 2 Gy. This represents a much larger tolerance in the partial irradiation of the liver compared with whole-liver irradiation. We have seen transient elevation of serum transaminases after liver irradiation, but we have not seen any symptomatic RILD. This absence in our series confirms that the liver can tolerate high-dose partial volume irradiation.

Cheng *et al.* (18) found that HCC patients who were hepatitis B virus carriers or had Child-Pugh Class B cirrhosis presented with a significantly greater susceptibility to radiation-induced liver dysfunction after three-dimensional conformal radiotherapy. Considering that Asian patients with HCC usually suffered from viral hepatitis, dose distribution for the liver is crucial to the preservation of hepatic function. Dawson *et al.* (16) showed that the mean liver doses associated with a 5% risk of classic RILD for primary and metastatic liver cancer are 28 Gy and 32 Gy, respectively, at 2 Gy per fraction. Considering the lower dose tolerance of liver in patients with HCC, RTRT's benefit of reducing irradiation to the normal liver would be more apparent for primary HCC than for metastatic liver cancers.

It is well known that the GI tract is an important serial organ that is at risk in liver irradiation anatomically. In the recent literature, liver irradiation was not associated with serious adverse GI effects. Park *et al.* (14) reported a 5.1% complication rate of localized X-ray therapy for gastric or duodenal ulcer. Yang *et al.* (5) reported that out of 153 patients with HCC treated with radiotherapy, radiation-induced ulcers were found in the stomach (n = 9) and duodenum (n = 14), and bleeding was found in 11 patients (7%), including 1 case of fatal bleeding. We have experienced a single case (1 of 15; 6%) of Grade 3 but transient gastric ulcer; this rate was equivalent to that in the previous series. Yang *et al.* reported 35% hematologic toxicity and 2% pneumonitis. Considering the shorter treatment time and higher daily dose used in the present study, the equivalently low complication rate in our series may be attributable to the high-precision radiotherapy obtained by using RTRT.

Kawashima *et al.* (19) reported on proton treatment for 31 patients with HCC. During a median follow-up period of 31 months (range, 16–54 months), only 1 patient experienced recurrence of the primary tumor, and the 2-year actuarial local progression-free rate was 96% (95% confidence interval [CI] 88%–100%). The actuarial overall survival rate at 2 years was 66% (95% CI 48%–84%). Chiba *et al.* (6) of Tsukuba University reported on 192 HCCs in 162 patients treated with a proton beam at 72 Gy (range, 55–84 Gy) with a follow-up period of 32 months (range, 3–133 months) and found 86.9% local control and 23.5% overall survival at 5 years. Obviously, proton therapy is one of the best solutions using focal radiotherapy in dose distribution. Proton therapy using a real-time tumor-tracking system will become a radical treatment for HCC.

In conclusion, RTRT provided effective focal high doses to liver tumors adjacent to the critical organs or to tumors that are located too deep for other treatments. Because the fiducial markers for RTRT need not be implanted into the tumor itself, RTRT can be applied to HCC in patients who are not candidates for other surgical or nonsurgical treatments.

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HBe抗原陽性例に対する治療

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はじめに

2006年9月にエンテカビルがB型慢性肝炎に保険適用となり、B型慢性肝炎治療が新たな時代に入った感がある。

B型慢性肝疾患はC型と異なり、様々な病態が存在する。またその経過も様々であるが、大別すると肝硬変、肝細胞癌に進行する群と、臨床的治癒の状態に落ち着く群に二分される。約80%は後者になると考えられるが、予後改善にはHBe抗原の陰性化とHBV DNAの低値持続が必要であり、そのためには適切な抗ウイルス治療が肝要となる。本稿ではHBe抗原陽性B型慢性肝炎に対する抗ウイルス治療の現状について述べる。

■HBステージ分類

HBVキャリアのそれぞれが現在どのような病期にあるのか、発癌リスクはどの程度なのか、積極的な治療の必要性はあるのか、そしてあるならどのような治療を選択すべきかという問いに明確に対処すべく、筆者らはHBVキャリアのステージ分類(**表1**)を提唱した[1]。

HBステージ「0」:HBe抗原陽性、ALT正常値持続のいわゆる無症候性キャリアの状態。

HBステージ「Ⅰ」:HBe抗原陽性、ALT異常値(持続正常以外)でHBV DNA量が$10^{7.6}$copies/mL以上の高ウイルス群、若年例(男性:30歳未満、女性:35歳未満)をステージ「Ⅰa」、高年例(男性:30歳以上、女性:35歳以上)をステージ「Ⅰb」とする。

HBステージ「Ⅱ」:HBe抗原陽性、ALT異常値(持続正常以外)でHBV DNA量が$10^{7.6}$copies/mL未満の低ウイルス群、若年例をステージ「Ⅱa」、高年例をステージ「Ⅱb」とする。

HBステージ「Ⅲ」:HBe抗原陰性、HBV DNA量が10^5copies/mL以上のプレコア変異株の増殖が持続していると考えられる群である。

HBステージ「Ⅳ」:HBe抗原陰性、HBV DNA量が10^5copies/mL未満のいわゆる臨床的治癒の状態である。

HBステージ「V」:HBVキャリア(HBs抗原陽性の時期が確認されている例)でHBs抗原が消失した状態である。

各ステージにおける初診時の血小板数と発癌率は**図1**のとおりである。発癌率はステージⅢ、Ⅱb、Ⅰbの順に高く、肝硬変進展も同様であった。これら肝硬変進展・肝癌発癌ハイリスク群は速やかな抗ウイルス治療導入の必要があり、HBe抗原陽性例ではステージⅠbおよびⅡb例に対するエンテカビル投与が第1選択と考えられる。また、ステージⅠaおよびⅡa例でも高度の炎症が持続し、早期の肝硬変進展が危惧される症例にはインターフェロン(IFN)治療を考慮すべきである。

■米国肝臓学会の治療指針

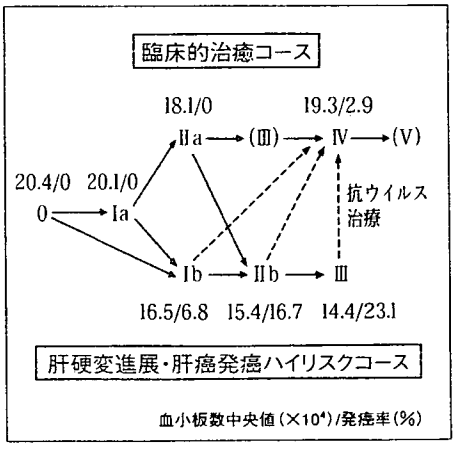
KeeffeらのUS Algorithm[2](**表2**)によると、HBe抗原陽性例に対して「5.0 log copies/mL未満のALT正常例は、原則的には無治療で6～12カ月ごとに経過観察、ただし、組織学的進展例に対しては治療を考慮する。5.0 log copies/mL以上のALT正常例については、特に35～40歳以上では肝生検を実施し、活動性の病変がある場合、あるいはALTの増加が認められた場合は治療を行う。製剤としてはアデホビル、エンテカビルあるいはPEG-IFN α-

表1 HBVキャリアのステージ分類

HBステージ	0	Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ
HBsAg	+	+	+	+	+	−**
HBeAg	+	+	+	−	−	−
HBV DNA (copies/mL)	不問	≧$10^{7.6}$	＜$10^{7.6}$	≧10^5	＜10^5	不問
ALT	持続正常	持続正常以外	持続正常以外	不問	不問	不問
年齢	不問	若年/高年*(Ⅰa/Ⅰb)	若年/高年*(Ⅱa/Ⅱb)	不問	不問	不問
発癌リスク	きわめて小	小／大	小／きわめて大	きわめて大	きわめて小	きわめて小

*若年:男性30歳未満、女性35歳未満、高年:男性30歳以上、女性35歳以上　**HBsAg(+)の時期が確認されていること

図1 HBVキャリアの経過(臨床的治癒コースと肝硬変進展・肝癌発癌ハイリスクコース)



2aを用いる。5.0 log copies/mL以上のALT異常例に対しては、アデホビル、エンテカビルあるいはPEG-IFNα-2aを用いて治療を行う。HBV DNA量高値の場合は、PEG-IFN α-2aよりもアデホビルかエンテカビルがより適用となる」とされている。

わが国では、アデホビル単独治療、PEG-IFNα-2aがともに、現在、保険適用になっておらず、若年例にはIFN 6カ月投与、高年例にはエンテカビルが第1選択薬になると考えられる。

■インターフェロン

従来の製剤のHBe抗原陽性例に対する国内IFN治療成績の集計[3]によると、4週投与例では投与終了1年後、2年後のHBe抗原陰性化率はそれぞれ29%、55%、HBe抗原抗体seroconversion率は12%、29%で、自然経過よりも高率としている。筆者らもHBe抗原陽性例23例(年齢中央値36.3歳)に対するPEG-IFN α-2a 9MU 3日間連日投与後、18MU 25日間連日投与(計477MU)にて、投与終了1年後のHBe抗原陰性化率50.0%、ALT正常化率36.8%およびHBV DNA陰性化率41.2%と良好な成績[4]を得ている。4週投与でも若年例の場合は有効性が高いと考えられる。

24週の長期投与は2000年4月より可能となった。再び国内IFN治療成績の集計によると、投与終了6カ月後のHBe抗原陰性化率は4週投与、24週投与でそれぞれ11%、28%と長期投与の有効性が確認されている。欧米では6カ月投与が標準投与法であるが、Wongら[5]はメタアナリシスの結果から投与終了後6カ月の時点でのHBe抗原陰性化率は33%で、自然経過の場合の12%に比し有意に高率であったとしている。

PEG-IFN α-2aに関してはLauら[6]が、HBe抗原陽性例においてラミブジン単独投与群に比し、PEG-IFN α-2a単独投与群およびPEG-IFN α-2a、ラミブジン併用投与群が有意に、HBe抗原抗体seroconversion率、HBe抗原陰性化率およびALT正常化率が高率であったと報告している。わが国では2007年にPEG-IFN α-2a単独の治験が開始される予定である。特に核酸アナログ剤が投与し難い若年例に対して、できるだけ早く保険適用になることが熱望される。

■ラミブジン

2000年11月に保険適用となって以来、現在までに約3万人のB型慢性肝炎、肝硬変症例に投与された。国内外で発癌抑止効果が報告[7,8]されているが、YMDD変異株(変異株)が高率に出現する。

当院でラミブジンを投与した後1年以上経過した99例(男性78例、年齢中央値45.6歳、女性21例、年齢中央値51.8歳)における成績では、HBe抗原陽性例(59例)のHBe抗原消失率、HBV DNA陰性化率(300 copies/mL未満)およびALT正常化率(基準値上限未満)は、それぞれ20.0%、47.3%および72.7%、HBe抗原陰性例(40例)ではHBV DNA陰性化率、ALT正常化率はそれぞれ76.3%、79.5%とHBe抗原陰性例でより良好な成績であった。また、投与開始前と1年後の組織学的推移が検討できた53例についてみ

表2 HBe抗原陽性例に対するKeeffeらのUS Algorithm

HBV DNA (log_{10} copies/mL)	ALT	治療指針
<5.0	正常	無治療
≧5.0	正常	進行例は治療 (エンテカビル, アデホビル, PEG-IFN α-2a)
≧5.0	高値	エンテカビル, アデホビル, PEG-IFN α-2a

ると、壊死、炎症を表すgrading、線維化を表すstagingはともに、1年の投与で有意(それぞれp<0.0001, p<0.01)に改善した。変異株検出率(全対象)は投与1年後7.2%、1.5年後23.3%、2年後38.2%と、2年後に高率に出現した。HBe抗原陽性例と陰性例の比較では、投与1年後、1.5年後および2年後の変異株出現率は、HBe抗原陽性例でそれぞれ6.7%、36.7%および53.3%、HBe抗原陰性例でそれぞれ7.9%、10.0%および20.0%と、HBe抗原陽性例で有意(1.5年後、2年後それぞれp<0.05)に高率であった。

■エンテカビル

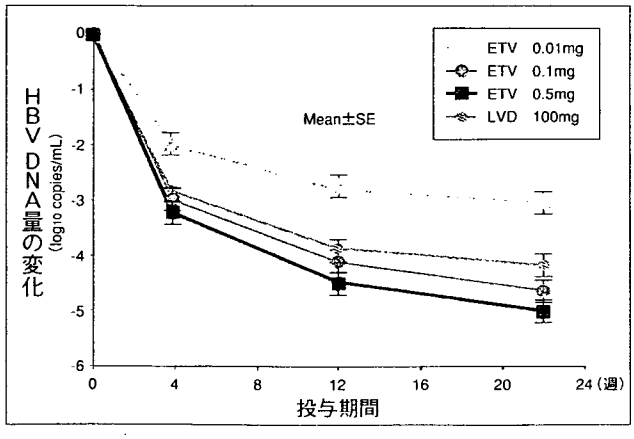
エンテカビルはラミブジンと同様に核酸アナログ剤で、2006年9月に保険適用となった。核酸アナログ未治療例には0.5mg/day、ラミブジン不応例には1mg/dayが常用量とされ、吸収率の点より空腹時に服用することが必要とされている。

国内治験(3試験)の報告[9](**図2、3**)によると、用量相関試験(24週)では、エンテカビル0.5mg投与群はラミブジン100mg投与群に比しHBV DNA変化量(log copies/mL)が有意に大(−5.16 vs −4.29)であった。未治療例対象試験では、エンテカビル0.5mg群において48週投与でHBV DNA平均変化量は−4.84、ALT正常化率は93.8%、HBe抗原陰性化率は29.6%であり、組織学的にも、壊死・炎症、線維化ともに有意な改善が認められた。また、ラミブジン不応例に対する1mg投与群では、HBV DNA平均変化量は−3.75、ALT正常化率は78.4%、HBe抗原陰性化率は15.2%であった。有害事象はほとんどが軽微で一過性であった。

海外では、Changら[10]が、核酸アナログ未治療のHBe抗原陽性例に対するラミブジンとのrandomised double-blind trial(二重盲検化試験)において、ラミブジンに比し組織学的改善度(72% vs 62%; p<0.01)、HBV DNA陰性化率(67% vs 36%; p<0.001)(**図4**)およびALT正常化率(68% vs 60%; p<0.05)が有意に良好であったことを報告している(48週)。また、Shermanら[11]はラミブジン不応のHBe抗原陽性例に対するラミブジンとの二重盲検化試験(エンテカビルは1mg/day)においても同様の報告(組織学的改善度、HBV DNA陰性化率およびALT正常化率いずれもp<0.0001 vsラミブジン)をしている。

エンテカビル変異株に関しては、2006年の米国肝臓学会での発表によると、核酸アナログ未治療例では48週服用後0.1%、ラミブジン抵抗例では1%にエンテカビル遺伝子型耐性を伴うウイルス量のリバウンドがみられている。

図2 エンテカビル3用量およびラミブジン100mgによる用量相関試験におけるHBV DNA変化量



■アデホビル

アデホビル単独治療は、現在治験中で保険適用にはなっていない。しかし、欧米ではHBe抗原陽性例に対する有効性が報告されている。Marcellinら[12]はアデホビル10mg、48週投与で組織学的改善、HBV DNA、ALT値の低下およびHBe抗原抗体seroconversion率の上昇を、また、3年(144週)投与[13]にて53%でHBe抗原消失、46%でHBe抗原抗体seroconversion、48%でHBV DNA陰性化を認めている。アデホビル変異株(N236T、A181V/T)検出率についてHadziyannisら[14]は、4〜5年投与例において、2年3%、3年11%、4年18%および5年29%と報告している。アデホビル変異株にはラミブジンやエンテカビルが有効と考えられている[15]。ラミブジン、アデホビル併用治療無効例も存在するが、それらに対するテノホビルの有効性が報告[16]された。テノホビルは現在、HIV感染症に承認されている薬剤であるが、B型慢性肝炎にも緊急避難的には使用を考慮すべきと考える。

図3　未治療例およびラミブジン不応例に対するエンテカビルに投与によるHBV DNA変化量

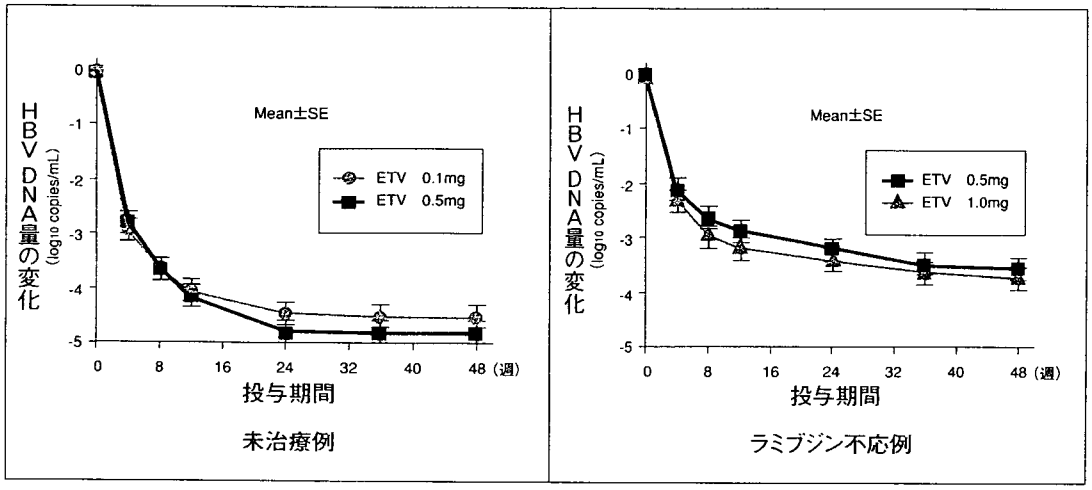
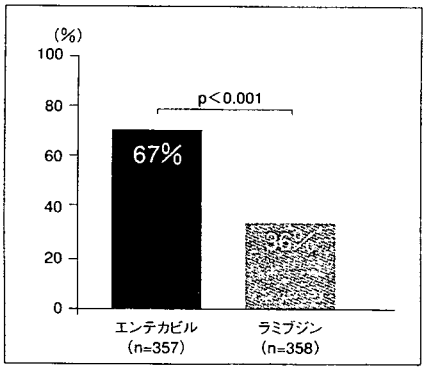


図4　HBe抗原陽性例に対する
エンテカビル、ラミブジン比較試験に
おけるHBV DNA陰性化率



おわりに

これまでIFN、ラミブジンおよびアデホビルが保険適用剤であったが、2006年9月よりエンテカビルが保険適用となり、B型慢性肝炎に対する抗ウイルス治療も新しい局面を迎えた。B型はC型に比し治療対象の選択がより重要で、それぞれの対象に対する適切な治療方法の選択と的確な治療の遂行が肝不全や発癌を防止し、予後の改善に寄与すると考えられる。

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