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Survey of survival among patients with hepatitis C virus-related hepatocellular carcinoma treated with peretinoin, an acyclic retinoid, after the completion of a randomized, placebo-controlled trial

Kiwamu Okita · Namiki Izumi · Kenji Ikeda · Yukio Osaki · Kazushi Numata · Masafumi Ikeda ·
Norihiro Kokudo · Kazuho Imanaka · Shuhei Nishiguchi · Shunsuke Kondo · Yoichi Nishigaki ·
Susumu Shiomi · Kazuomi Ueshima · Norio Isoda · Yoshiyasu Karino · Masatoshi Kudo · Katsuaki Tanaka ·
Shuichi Kaneko · Hisataka Moriwaki · Masatoshi Makuuchi · Takuji Okusaka · Norio Hayashi ·
Yasuo Ohashi · Hiromitsu Kumada · The Peretinoin Study Group

Abstract

Background This study examined the effects of peretinoin, an acyclic retinoid, on the survival of patients with hepatitis C virus-related hepatocellular carcinoma (HCC) who had completed curative therapy and participated in a randomized, placebo-controlled trial.

Methods This study was an investigator-initiated retrospective cohort study. Subjects were all patients who were administered the investigational drug (peretinoin 600 mg/day, peretinoin 300 mg/day, or placebo) in the randomized trial. Survivals between the groups were compared using the log-rank test, and hazard ratios were estimated by Cox regression.

Results Survey data were collected from all patients ($n = 392$) who participated in the randomized trial, all of whom were then divided into the peretinoin 600 mg/day ($n = 132$), peretinoin 300 mg/day ($n = 131$), and placebo ($n = 129$) groups. At the median follow-up of 4.9 years, 5-year cumulative survival rates for patients in the 600 mg/day, 300 mg/day, and placebo groups were 73.9, 56.8, and 64.3 %, respectively. Comparison of overall survival among patients classified as Child-Pugh A revealed that

K. Okita (✉)
Shimonoseki Kohsei Hospital, Kamishinchi-Machi 3-3-8,
Shimonoseki, Yamaguchi 750-0061, Japan
e-mail: icb68895@nifty.com

N. Izumi
Musashino Red Cross Hospital, Sakai-minami-cho 1-26-1,
Musashino, Tokyo 180-8610, Japan

K. Ikeda · H. Kumada
Toranomon Hospital, Toranomon 2-2-2, Minato-ku,
Tokyo 105-8470, Japan

Y. Osaki
Osaka Red Cross Hospital, Fudegasaki-cho 5-30, Tennoji-ku,
Osaka 543-8555, Japan

K. Numata · K. Tanaka
Yokohama City University Medical Center, Urafune-cho 4-57,
Minami-ku, Yokohama 232-0024, Japan

M. Ikeda
National Cancer Center Hospital East, Kashiwanoha 6-5-1,
Kashiwa, Chiba 277-8577, Japan

N. Kokudo
The University of Tokyo Hospital, Hongo 7-3-1, Bunkyo-ku,
Tokyo 113-8655, Japan

K. Imanaka
Osaka Medical Center for Cancer and Cardiovascular Diseases,
Nakamichi 1-3-3 Higashinari-ku, Osaka 537-8511, Japan

S. Nishiguchi
Hyogo College of Medicine Hospital, Mukogawa-cho 1-1,
Nishinomiya, Hyogo 663-8501, Japan

S. Kondo · T. Okusaka
National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku,
Tokyo 104-0045, Japan

Y. Nishigaki
Gifu Municipal Hospital, 7-1 Kashima-cho, Gifu 500-8513,
Japan

S. Shiomi
Osaka City University Hospital, Asahi-machi 1-5-7, Abeno-ku,
Osaka 545-8585, Japan

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survival of the 600 mg/day group ($n = 105$) was significantly longer than that of the placebo group ($n = 108$) (hazard ratio 0.575, 95 % CI 0.341–0.967; $P = 0.0347$).

Conclusions Administration of 600 mg/day peretinoin to patients with hepatitis C virus-related HCC who have completed curative therapy may improve survival for those classified as Child-Pugh A, for whom liver function is relatively stable.

Keywords Hepatocellular carcinoma · Hepatitis C virus · Multicentric carcinogenesis · Overall survival · Peretinoin

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world, affecting 740,000 people annually [1]. The incidence of HCC has been rising due to an increase in hepatitis C virus (HCV) infections [2–4]. HCC comprises 94 % of all primary liver cancers in Japan; one prominent cause is infection by HCV [4]. Hepatitis C virus-related HCC (HCV-HCC) comprises 75 % of all HCC cases, while HCC due to hepatitis B virus infection (HBV-HCC) comprises 10–15 % [5].

Early diagnosis and curative treatment for HCC, such as hepatectomy or radiofrequency ablation (RFA, a localized therapy), has become more prevalent in recent years.

K. Ueshima · M. Kudo
Kinki University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan

N. Isoda
Jichi Medical University, Yakushiji 3311-1, Shimotsuke-shi, Tochigi 329-0498, Japan

Y. Karino
Sapporo Kosei General Hospital, Kita 3-jo Higashi 8-choume-5, Chuo-ku, Sapporo, Hokkaido 060-0033, Japan

S. Kaneko
Kanazawa University Hospital, Takara-machi 13-1, Kanazawa, Ishikawa 920-8641, Japan

H. Moriwaki
Gifu University Hospital, Yanagido 1-1, Gifu 501-1194, Japan

M. Makuuchi
Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo 150-8935, Japan

N. Hayashi
Kansai Rosai Hospital, Inabaso 3-1-69, Amagasaki, Hyogo 660-8511, Japan

Y. Ohashi
Chuo University, Kasuga 1-13-27, Bunkyo-ku, Tokyo 112-8551, Japan

However, high recurrence rates and unfavorable prognoses remain even after curative treatment for HCV-HCC. Cumulative recurrence rates of HCV-HCC are high, with reported rates of 24, 76, and 92 % at 1, 3, and 5 years, respectively, after treatment for the initial onset of liver cancer [6]. Characteristics of HCC recurrence include metastases within the liver, and many patients experience multicentric cancer onset due to underlying liver conditions (e.g., cirrhosis) related to viral liver disease. As underlying liver disease can provide optimal sites for oncogenesis, suppression of multicentric cancer onset is particularly important for improving HCC prognosis, even after curative treatment. Hepatitis virus-related HCC is often treated effectively by antiviral therapies such as interferon [7–9]. However, strategies to control recurrence following cured HCC have not yet been established [10–12].

One method used to control cured HCC recurrence employs a retinoid-based chemoprevention strategy [13]. Peretinoin [(2*E*,4*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,4,6,10,14-pentaenoic acid] is a retinoid with a vitamin A-like structure discovered by Muto et al. (1980) [14], and currently is one of the potential drugs anticipated to suppress HCC recurrence [15–17].

According to a randomized trial [18], administration of 600 mg/day peretinoin suppressed HCV-HCC recurrence following curative therapy. In Japan, 75 % of patients with HCC test positive for HCV, and compared to other causes of HCC, HCV has the highest risk of recurrence. Thus, the randomized trial aimed to examine the suppressive effects of peretinoin on recurrence among a population with a homogeneously high risk for recurrence, and thus focused on patients who tested positive for HCV following curative therapy. The trial was a multicenter, parallel-group, double-blind, randomized, placebo-controlled trial. Patients who tested positive for HCV (negative for HBV) and underwent liver resection or RFA to treat initial onset or initial recurrence, and who were classified as Child-Pugh A or B, were assigned to one of the following three groups: peretinoin 600 or 300 mg/day, or placebo. The investigational drug was administered orally once a day, for no longer than 2 years. Of the 401 patients registered in the randomized trial between March 2005 and July 2007, 268 were administered the investigational drugs (peretinoin 600 mg/day, $n = 134$; peretinoin 300 mg/day, $n = 134$; placebo, $n = 133$). Our analysis revealed no superiority of the treatment groups (peretinoin 600 and 300 mg/day) over the placebo group with respect to the primary endpoint of recurrence-free survival ($P = 0.434$). However, the highest 3-year cumulative recurrence-free survival rate (43.7 %) was found in the group administered 600 mg/day peretinoin. The peretinoin 600 mg/day group also showed a significantly lower recurrence rate after 2 years relative to that of the placebo group (hazard ratio 0.27; 95 % CI

0.07–0.96). Sub-group analysis revealed that within the peretinoin 600 mg/day group, the recurrence risk also decreased significantly among those classified as Child-Pugh A (hazard ratio to the placebo group, 0.60; 95 % CI 0.41–0.89) and those with tumor size under 2 cm (hazard ratio to the placebo group, 0.41; 95 % CI 0.23–0.73). Notably, the follow-up duration for the randomized trial was short (median, 2.5 years), and we did not evaluate overall survival among groups.

This study was conducted as an investigator-initiated research, independently of the randomized trial to evaluate the effects of peretinoin on the overall survival up to 6 years of follow-up.

Methods

Study design

This study was a retrospective cohort study which assessed survival outcomes of all participating patients to the randomized trial from the time the trial ended through December 31, 2011. The randomized trial was conducted in accordance with Good Clinical Practice guidelines.

Setting and participants

The principal investigator obtained permission to conduct the study from the ethics committee of Shimonoseki Kohsei Hospital. Approval for data provision was obtained in accordance with the respective institution's regulations. The study was conducted in compliance with the Declaration of Helsinki, as well as the "Ethical Guidelines for Epidemiological Research" set in Japan by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare.

Of the 41 medical institutions where the randomized trial was conducted, we targeted all the institutions that provided written consent to participate in this cohort study and used a data collection form to collect data in the medical records. The collected data included the dates of any deaths up through December 31, 2011 and the last recorded date of survival (in cases where observation was not possible). Data collection forms were collected between January 1, 2012 and December 31, 2012. Data collection forms were mailed from the data center to the medical institutions providing the data. At the medical institutions providing the data, either the physician in charge of the study or the person delegated by this physician provided answers to the questions according to existing resources (medical records, etc.). Anonymized data collection forms were then sent back to the data center.

The primary endpoint was overall survival, defined by the time period beginning on the date of patient registration for the randomized trial until death from all causes or the final date when survival was confirmed. Patients for whom survival was last confirmed before December 2011 were treated as "lost to follow-up."

At the medical institutions providing the data, if a delegate of the physician in charge of the study completed the data collection form, the physician validated the data such that data reliability was guaranteed. The data center conducted an independent and careful review of the collected data according to the data management plan, and then created and maintained the database.

Statistical analysis

In accordance with the principle of the intention-to-treat analysis, this study analyzed data from all patients who had been administered the investigational drug in the randomized trial. Cumulative survival rates in each treatment group were calculated by the Kaplan–Meier method with the dates of each patient registration for the randomized trial as the starting point. The log-rank test was used to compare the 600 mg/day peretinoin and placebo groups, and the 300 mg/day peretinoin and placebo groups. We also calculated hazard ratios and 95 % confidence intervals (CIs) using the Cox proportional hazards model. Two-tailed statistical significance was set at $P < 0.05$, and P values were not adjusted for multiplicity. All data from December 31, 2011 onwards were treated as censored.

In sub-group analyses, the same survival time analysis method used to evaluate primary endpoints was employed on the classification factors which were set in advance. Classification factors included Child-Pugh classification (A, B), tumor size (<2 cm, ≥ 2 cm), curative treatment procedure (local ablation, resection), sex (male, female), and age when consent was provided (<65 years, 65–74 years, ≥ 75 years). All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). This study is registered in the UMIN Clinical Trials Registry (UMIN000006728).

Results

Patients

Survey data were collected from all 392 patients (600 mg/day, $n = 132$; 300 mg/day, $n = 131$; placebo, $n = 129$) (Fig. 1). Patient demographic factors are summarized in Table 1. Sex, age, treatment approach, Child-Pugh classification, and primary tumor size were well balanced among the three treatment groups. Number of deaths in the
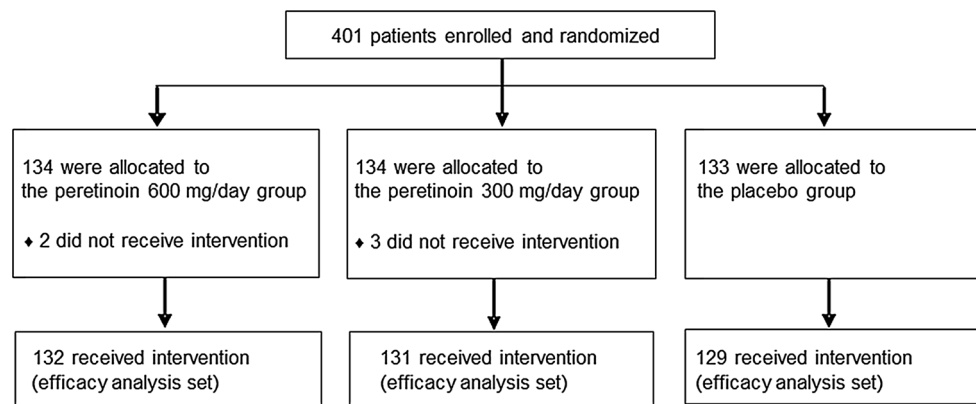
Fig. 1 Flow diagram of patient selection. For the randomized trial, a total of 401 individuals were registered and assigned randomized treatments (peretinoin 600 mg/day, $n = 134$; peretinoin 300 mg/day, $n = 134$; placebo, $n = 133$). Of these, those who were ultimately not administered the investigational drug (2 in the 600 mg/day group, 3 in the 300 mg/day group, and 2 in the placebo group) were excluded, and data from the remaining patients were analyzed (peretinoin 600 mg/day, $n = 132$; peretinoin 300 mg/day, $n = 131$; placebo, $n = 129$)

Table 1 Patient demographics

	Peretinoin		Placebo ($n = 129$)	P value (χ^2)
	600 mg/day ($n = 132$)	300 mg/day ($n = 131$)		
Sex				
Male	85 (64.4 %)	76 (58.0 %)	89 (69.0 %)	0.1806
Female	47 (35.6 %)	55 (42.0 %)	40 (31.0 %)	
Age (years)[a]				
<65	38 (28.8 %)	42 (32.1 %)	41 (31.8 %)	0.7331
65–74	69 (52.3 %)	62 (47.3 %)	57 (44.2 %)	
≥75	25 (18.9 %)	27 (20.6 %)	31 (24.0 %)	
Curative treatment				
Local ablation	85 (64.4 %)	84 (64.1 %)	85 (65.9 %)	0.9497
Resection	47 (35.6 %)	47 (35.9 %)	44 (34.1 %)	
Child-Pugh				
A	105 (79.5 %)	107 (81.7 %)	108 (83.7 %)	0.6842
B	27 (20.5 %)	24 (18.3 %)	21 (16.3 %)	
Tumor size				
<2 cm	58 (43.9 %)	58 (44.3 %)	59 (45.7 %)	0.9531
≥2 cm	74 (56.1 %)	73 (55.7 %)	70 (54.3 %)	

[a] Age at the time of registration in the randomized trial

600 mg/day group, the 300 mg/day group, and the placebo group were 36, 55, and 47, respectively. In the 600 mg/day group, the 300 mg/day group, and the placebo group, 19, 15, and 15 patients, respectively, were "lost to follow-up."

The median follow-up duration was 1,782 days (4.9 years), with a maximum of 2,364 days (6.5 years). Median and maximum follow-up durations for each of the groups were as follows: 1,815 days (5.0 years) and 2,364 days (6.5 years) for the 600 mg/day group, 1,681 days (4.6 years) and 2,320 days (6.4 years) for the 300 mg/day group, and 1,768 days (4.8 years) and 2,336 days (6.4 years) for the placebo group.

Overall survival

Table 2 shows cumulative survival rates determined using the Kaplan–Meier method. The 2-year survival rates in the 600 mg/day, 300 mg/day, and placebo groups were 93.1, 88.5, and 93.0 %, respectively. The 5-year survival rates in the 600 mg/day, 300 mg/day, and placebo groups were

Table 2 Patients with follow-up and survival rates

Group	n	Censored[a]	Event[c]	Survival rate	
				2 years	5 years
600 mg/day	132	96 (19[b])	36	93.1 %	73.9 %
300 mg/day	131	76 (15[b])	55	88.5 %	56.8 %
Placebo	129	82 (15[b])	47	93.0 %	64.3 %

Median follow-up time: 4.9 years

[a] Data from after 12/31/2011 were considered censored cases

[b] If the last date on which survival was confirmed was before December of 2011, then the patient was considered lost to follow-up

[c] Death due to any cause was considered an event

73.9, 56.8, and 64.3 %, respectively, with the maximum cumulative survival rate observed in the 600 mg/day group. Median survival time in the 300 mg/day and placebo groups were 2,102 days (5.8 years) and 2,165 days (5.9 years), respectively; this parameter could not be calculated for the 600 mg/day group due to good prognosis. Figure 2 shows the Kaplan–Meier curves for the 600 mg/day and placebo groups. With regard to overall survival, no significant difference was observed between the 600 mg/day and placebo groups (hazard ratio 0.726; 95 % CI 0.470–1.122; $P = 0.1475$ by the log-rank test). Similarly, no significant difference in overall survival was observed between the 300 mg/day and placebo groups (hazard ratio 1.253; 95 % CI 0.849–1.850; $P = 0.2547$ by the log-rank test).

Sub-group analysis (600 mg/day vs. placebo group)

Results from the sub-group analysis of survival time, which compared the 600 mg/day and placebo groups, are shown in Fig. 3. Factors from the sub-group analysis that were significant at the $P < 0.05$ level by the log-rank test included the Child-Pugh A classification (hazard ratio 0.575; 95 % CI 0.341–0.967; $P = 0.0347$ by the log-rank test) and primary tumor size under 2 cm (hazard ratio 0.447; 95 % CI 0.218–0.919; $P = 0.0245$ by the log-rank test). Kaplan–Meier curves by Child-Pugh A classification for the 600 mg/day and placebo groups (600 mg/day, $n = 105$; placebo, $n = 108$) are shown in Fig. 4.

Discussion

Early diagnosis and curative treatment for HCC has become widespread, but following completion of curative treatment for HCV-HCC, recurrence rates remain high and prognosis is poor. The 5-year cumulative survival rate in this cohort study was higher in the 600 mg/day peretinoin group than in the placebo group. Particularly for patients with the Child-Pugh A classification, the 600 mg group had significantly longer survival compared to the placebo group. We believe that this finding will contribute to future attempts for developing measures to prevent HCC recurrence.

The guidelines for clinical studies of HCC [19] recommend that only patients with the Child-Pugh A classification be incorporated into clinical studies, because death due to cirrhosis among patients classified as Child-Pugh B or Child-Pugh C could mask treatment effects. In this study, roughly 80 % of our patients were classified as Child-Pugh A, and thus our results relating to this group may be generalizable. In addition, the results of this study, expressed in patients with tumor size of under 2 cm, are consistent with the report of Nakashima et al. [20] that suggests the incidence of multicentric recurrence is high amongst

Fig. 2 Kaplan–Meier plot of overall survival: peretinoin 600 mg/day vs placebo. Hazard ratio 0.726; 95 % CI 0.470–1.122; $P = 0.1475$ by log-rank test
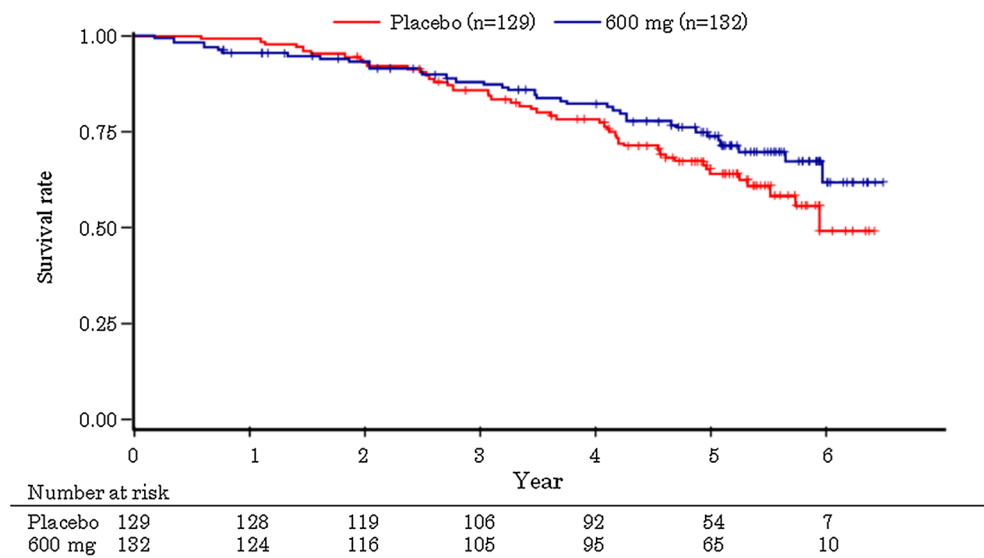

Number at risk							
	0	1	2	3	4	5	6
Placebo	129	128	119	106	92	54	7
600 mg	132	124	116	105	95	65	10

Fig. 3 Sub-group analysis: peretinoin 600 mg/day vs. placebo. †Age at the time of registration to the randomized trial. ‡Log-rank test

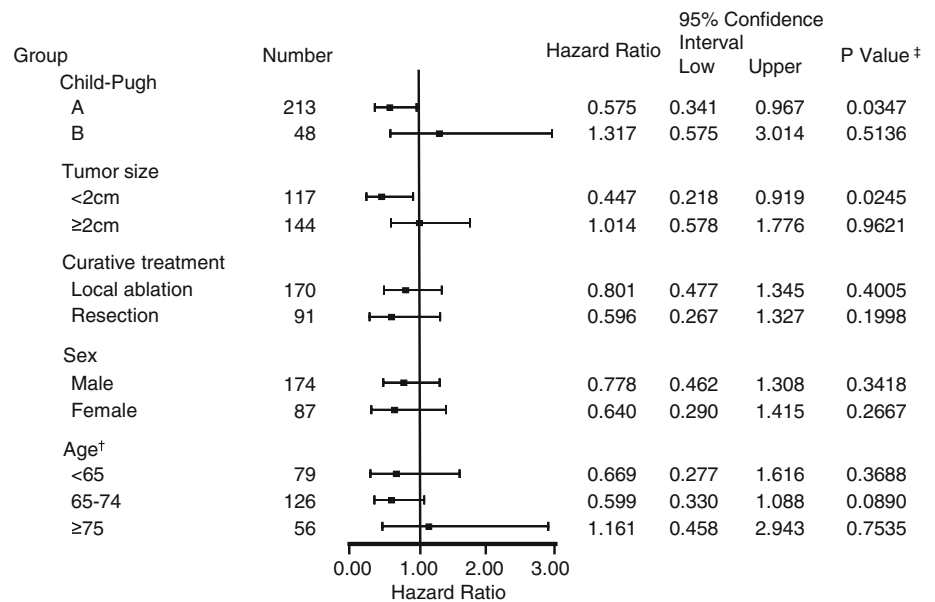| Group	Number	Hazard Ratio	95% Confidence Interval Low	Upper	P Value ‡
Child-Pugh					
A	213	0.575	0.341	0.967	0.0347
B	48	1.317	0.575	3.014	0.5136
Tumor size					
<2cm	117	0.447	0.218	0.919	0.0245
≥2cm	144	1.014	0.578	1.776	0.9621
Curative treatment					
Local ablation	170	0.801	0.477	1.345	0.4005
Resection	91	0.596	0.267	1.327	0.1998
Sex					
Male	174	0.778	0.462	1.308	0.3418
Female	87	0.640	0.290	1.415	0.2667
Age†					
<65	79	0.669	0.277	1.616	0.3688
65-74	126	0.599	0.330	1.088	0.0890
≥75	56	1.161	0.458	2.943	0.7535

Fig. 4 Kaplan–Meier plot of overall survival in Child-Pugh A: peretinoin 600 mg/day vs. placebo. Hazard ratio 0.575; 95 % CI 0.341–0.967; log-rank test, $P = 0.0347$

Number at risk	0	1	2	3	4	5	6
Placebo	108	107	100	88	75	47	7
600 mg	105	104	100	92	82	56	9
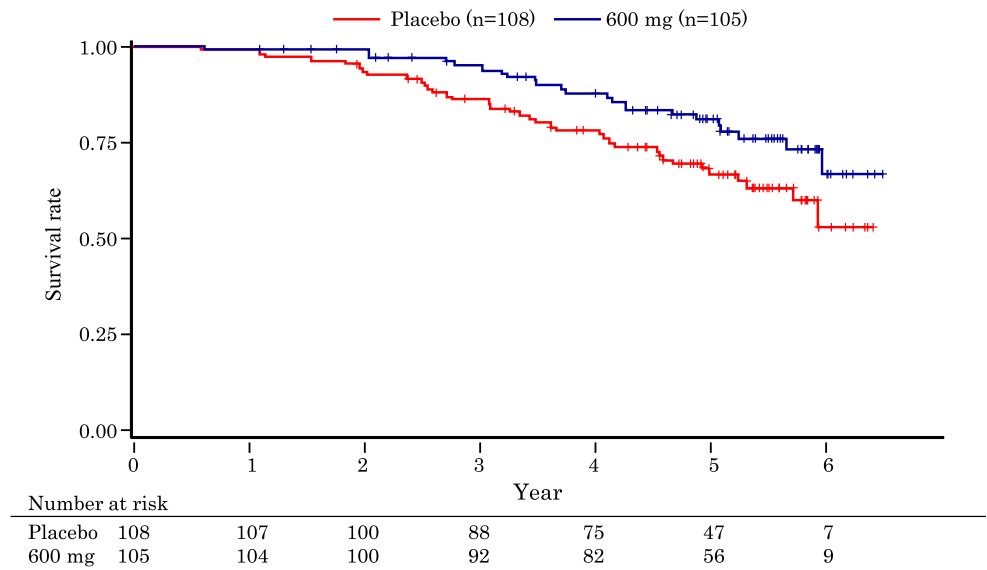
patients with tumor size of under 2 cm, and peretinoin is particularly effective at suppressing multicentric recurrence in such cases.

From the results of this study and the randomized trial, we speculate that peretinoin improves patient survival time by suppressing HCC recurrence. Among those classified as Child-Pugh A, the hazard ratio of recurrence-free survival for peretinoin and placebo in the randomized trial was 0.60 (95 % CI 0.41–0.89) [18], and the hazard ratio of overall survival for peretinoin 600 mg/day and placebo was 0.575 (95 % CI 0.341–0.967). The similar hazard ratios could be explained by the following reasons. First, the investigational drug was administered for 2 years maximum in the

randomized trial, and the median follow-up duration of this cohort study was nearly 5 years. Peretinoin is particularly well-known for its capacity to suppress multicentric recurrence, so given that a certain duration of time is required for a pre-cancerous lesion to develop into cancer, we surmise that peretinoin may have continued to work effectively in suppressing recurrence even after completion of peretinoin treatment. A follow-up survey [21] of the randomized trial conducted by Muto et al. [16] found that after administering this drug for 1 year, continued effects were noted for at least 150 weeks (roughly 3 years) following treatment completion. In addition, peretinoin has been found to suppress platelet-derived growth factor C

[22, 23], and thus it may be continuously suppressing recurrence by inhibiting the progression of hepatic fibrosis.

The limitation of this study was that the randomized trial was designed to evaluate recurrence-free survival in peretinoin-treated patients, and thus the number of patients may have been insufficient for evaluating the primary endpoint of this cohort study, i.e., overall survival. However, being able to collect and evaluate data from all patients who were administered the investigational drug in the randomized trial improved the statistical accuracy of our analysis.

Despite the limitation, the important point of this study is that by focusing on survival versus death, which is an index with no room for subjectivity, we were able to determine that among those classified as Child-Pugh A, the 600 mg/day group had a significantly longer overall survival compared to the placebo group. Notably, independent of this cohort study, a phase III trial is currently underway to examine the effects of peretinoin on controlling HCC recurrence among those classified as Child-Pugh A who have completed curative treatment for HCV-HCC. In conclusion, administration of 600 mg/day peretinoin to patients who have completed curative treatment for HCV-HCC is anticipated to improve survival of patients with relatively stable liver function, such as those classified as Child-Pugh A. Our finding provides novel insights into the understanding of 5-year survival after treatment with investigational drug in patients with HCV-HCC.

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